Risk Factors Comparison 2025-03-04 to 2024-03-04 Form: 10-K

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Investing in our common stock involves a high degree of risk. Before making your decision to invest in shares of our common stock, you should carefully consider the risks and uncertainties described below, together with the other information contained in this annual report, including our financial statements and the related notes and " Management' s Discussion and Analysis of Financial Condition and Results of Operations ". The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. We cannot assure you that any of the events discussed below will not occur. These events could have a material and adverse impact on our business, financial condition, results of operations and prospects. If that were to happen, the trading price of our common stock could decline, and you could lose all or part of your investment. Risks Related to Our Financial Position and Need for Additional Capital We are a clinical stage genetic medicines company with a history of operating losses, and we may not achieve or sustain profitability. We anticipate that we will continue to incur losses for the foreseeable future. Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability. We are a clinical stage genetic medicines company with a limited operating history on which to base your investment decision. Biotechnology product development is a highly speculative undertaking and involves a substantial degree of risk. Our operations to date have been limited primarily to staffing our company, business planning, raising capital, entering into collaboration and vendor agreements for conducting preclinical research and clinical development activities for our product candidates, and performing clinical development activities and manufacturing clinical supply. All of our product candidates are in the clinical development stage, have been **outlicensed** ~~stopped from further clinical development in order~~ to ~~reduce operating expenditures~~ **a third party**, or are in the preclinical or discovery stage. We have no products approved for commercial sale and have not generated any revenue from commercial product sales, and we will continue to incur significant research and development and other expenses related to our clinical development and ongoing operations. We have **generally** funded our operations to date through proceeds from sales of our convertible preferred stock, and public offerings, and do not expect to receive revenue **from commercial product sales,** for many years, if ever. We have incurred net losses since our inception in 2017. We incurred net losses of $ **64. 8 million and $** 102 ~~. 1 million and $ 136~~. 1 million for the ~~year~~ **years** ended December 31, **2024 and** 2023 ~~and 2022~~, respectively. As of December 31, ~~2023~~ **2024**, we had an accumulated deficit of $ ~~594~~ **659**. ~~5~~ **2** million. Substantially all of our operating losses have resulted from expenses incurred in connection with our research and development programs, acquiring the rights to our product candidates, and from general and administrative expenses associated with our operations. We expect to continue to incur significant expenses and operating losses over the next several years and for the foreseeable future as we intend to continue to conduct research and development, clinical testing, regulatory compliance activities, manufacturing activities, and, if any of our product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect that it will be several years, if ever, before we have a commercialized product. We anticipate that our expenses will increase substantially if, and as, we: • advance our product candidates from the preclinical or discovery stage to the clinical development stage; • advance our clinical product candidates into later stage clinical development; • seek regulatory approvals for any product candidates that successfully complete clinical trials; • hire additional clinical, quality control, regulatory, manufacturing, scientific and administrative personnel; • expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development, manufacturing and commercialization efforts; • **develop** ~~expand or build our~~ internal manufacturing capabilities; • maintain, expand and protect our intellectual property portfolio; and • incur additional legal, accounting or other expenses in operating our business, including the additional costs associated with operating as a public company. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We have never generated revenue from product sales and may never achieve or maintain profitability. We have no products approved for commercial sale and have not generated any revenue from commercial product sales. To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential, which will require us to be successful in a range of challenging activities. These activities can include completing preclinical studies and initiating and completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, obtaining coverage and adequate reimbursement from government and third- party payors, marketing, distributing, and selling those products that are approved and satisfying any post marketing requirements. 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. 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 or when, or if, we will be able to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable 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 you to lose all or part of your investment. We will need to raise additional funding before we can expect to become profitable from any potential future sales of our products. This additional financing 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 our product development efforts or other operations. We will require substantial future capital in order to complete planned and future preclinical and clinical development for our portfolio of product candidates and potentially commercialize these product candidates, if approved. If our product portfolio progresses into later stage clinical trials, or our current preclinical product candidates progress into the clinical trial stage, we expect our spending levels to significantly increase in connection with our continued clinical trial activities and production of our clinical product candidates' supply. 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. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Our ability to raise additional funds also depends on general financial, economic and market conditions as well as other factors, including financial institutions that may experience insolvency or financial distress ~~similar to that experienced by both Silicon Valley Bank and Signature Bank in March 2023,~~ over which we may have no or limited control. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate certain of our licensing activities, our research and development programs or other operations. Our operations have consumed significant amounts of cash since inception. As of December 31, ~~2023~~ **2024** , our cash, cash equivalents and marketable securities were $ ~~114~~ **76** . ~~3~~ **8** million. We expect that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the ~~fourth~~ **first** quarter of ~~2025~~ **2027** . However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect. ~~39Our~~ **37Our** future capital requirements will depend on many factors, including: ● the scope, timing, progress and results of discovery, preclinical development, laboratory testing and clinical trials for our product candidates; ● the expenses of manufacturing our product candidates for clinical trials and in preparation for marketing approval and commercialization; ● the extent to which we enter into collaborations or other arrangements with additional third parties in order to further develop our product candidates; ● the expenses of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property- related claims; ● the expenses and fees associated with the discovery, acquisition or in- license of additional product candidates or technologies; ● our ability to establish collaborations on favorable terms, if at all; ● the expenses required to scale up our clinical, regulatory and manufacturing capabilities; ● the expenses of future commercialization activities, if any, including establishing sales, marketing, manufacturing and distribution capabilities, for any of our product candidates for which we receive marketing approval; ● the availability of coverage and adequate reimbursement from government and third- party payors for our product candidates for which we receive marketing approval; and ● revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives, which may not be available to us on acceptable terms, or at all. **For example, we are party to the Sales Agreement with Cowen relating to the sale and issuance, from time to time, of shares of our common stock in at- the- market equity offerings with an aggregate offering price up to $ 50. 0 million, or the ATM Facility. However, our ability to raise capital under the ATM Facility or other registration statements may be limited by, among other things, SEC rules and regulations impacting the eligibility of smaller companies to use Form S- 3 for primary offerings of securities. Based on our public float, as of the date of the filing of this Annual Report on Form 10- K, we are only permitted to utilize a shelf registration statement, including the registration statement under which the ATM Facility is operated, subject to Instruction I. B. 6 to Form S- 3, which is referred to as the " baby shelf " rule. For so long as our public float is less than $ 75. 0 million, we may not sell more than the equivalent of one- third of our public float during any 12 consecutive months pursuant to the baby shelf rules. Although alternative public and private transaction structures may be available, these may require additional time and cost, may impose operational restrictions on us, and may not be available on attractive terms.** 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. If adequate funds are not available to us on a timely basis or on terms acceptable to us, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more product candidates or discovery stage programs or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize any product candidates, if approved. Raising 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 substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or securities convertible into equity, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends. ~~If~~ **38If** we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed or on terms acceptable to us, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. ~~40Risks~~ -- **Risks** Related to Product Development and Regulatory ApprovalPBFT02 is currently our sole clinical **-** stage product candidate and we may not be able to successfully develop and commercialize PBFT02. We are currently dependent on the potential development of a single clinical product

candidate, PBFT02. We are still developing our sole clinical product candidate, and PBFT02 cannot be marketed or sold in the United States or in foreign markets until regulatory approval has been obtained from the FDA or applicable foreign regulatory agencies. The process of obtaining regulatory approval is expensive and time consuming. The FDA and foreign regulatory authorities may never approve PBFT02 for sale and marketing, and even if PBFT02 is ultimately approved, regulatory approval may be delayed or limited in the United States or in other jurisdictions. Even if we are authorized to sell and market PBFT02 in one or more markets, there is no assurance that we will be able to successfully market PBFT02 or that PBFT02 will achieve market acceptance sufficient to generate profits. If we are unable to successfully develop and commercialize PBFT02 due to failure to obtain regulatory approval for PBFT02, to successfully market PBFT02 **or** , to generate profits from the sale of PBFT02 ~~, or~~ due to other risk factors outlined in this report, it would have material adverse effects on our business, financial condition, and results of operations. We are early in our development efforts. Our business is dependent on our ability to advance our current and future product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them. If we are unable, or experience significant delays in doing so, our business will be materially harmed. We are early in our clinical development efforts and our clinical product candidates are in early phase clinical trials. Additionally, we have a portfolio of programs that are in different stages of preclinical development and some may never advance to clinical stage development. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. We currently generate no revenue from sales of any product and we may never be able to develop or commercialize a marketable product. Each of our programs and product candidates will require additional preclinical and / or clinical development, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, capacity and expertise, building a commercial organization or successfully outsourcing commercialization, substantial investment and significant marketing efforts before we generate any revenue from product sales. Our product candidates must be authorized for marketing by the FDA, or certain other ex- U. S. regulatory agencies before we may commercialize our product candidates. The clinical and commercial success of our product candidates will depend on several factors, including the following: ● timely and successful completion of preclinical studies, including toxicology studies, biodistribution studies, biocompatibility studies and minimally efficacious dose studies in animals, where applicable; ● effective INDs or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for our product candidates; ● successful enrollment and completion of clinical trials, including under the international current Good Clinical Practices, or cGCPs, and current Good Laboratory Practices, or GLPs; ● positive results from our current and future clinical programs that support a finding of safety and effectiveness and an acceptable benefit- risk profile of our product candidates in the intended populations; ● receipt of marketing approvals from applicable regulatory authorities; **39** ● establishment of arrangements with third- party manufacturers or our own facilities for clinical supply and, where applicable, commercial manufacturing capabilities; ● establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates; ● commercial launch of our product candidates, if approved, whether alone or in collaboration with others; ● acceptance of the benefits and use of our product candidates, including method of administration, if and when approved, by patients, the medical community and third-party payors; ~~41~~ ● effective competition with other therapies; ● establishment and maintenance of healthcare coverage and adequate reimbursement and patients' willingness to pay out- of- pocket in the absence of such coverage and adequate reimbursement; ● establishment of a physician training system and network for administration of our product candidates by administration into the ICM; ● enforcement and defense of intellectual property rights and claims; and ● maintenance of a continued acceptable safety, tolerability and efficacy profile of our product candidates following approval. If we do not succeed in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. If we are unable to advance our product candidates to clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed. Preclinical and clinical development involve ~~a~~ lengthy and expensive ~~process~~ **processes** with ~~an~~ uncertain ~~outcome~~ **outcomes** . We may incur additional expenses or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our current product candidates or any future product candidates. All of our product candidates are in clinical or preclinical development and their risk of failure is high. We also rely on third- parties, **such as Gemma** ~~and currently primarily GTP~~ , for our preclinical and IND- enabling studies. It is impossible to predict when or if any of our product candidates will receive regulatory approval. To obtain the requisite regulatory approvals to commercialize any product candidates, we must demonstrate through extensive preclinical studies and lengthy, complex and expensive clinical trials that our product candidates are safe and effective in humans ~~. For example, our IND for PBGM01 for the treatment of GM1, for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring out- licensing opportunities for this asset, was initially placed on clinical hold. Even though the FDA removed the clinical hold on the IND for PBGM01, other future product candidates may be subject to clinical holds in the future~~ . Clinical testing can take many years to complete, and its outcome is inherently uncertain. We will rely on contract laboratories and other third parties, or our CROs, for the clinical development of our clinical product candidates. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials or early cohorts of our clinical trials of our product candidates, including early biomarker data, may not be predictive of the results of later- stage clinical trials or later cohorts of our clinical trials. Early clinical trials and in particular initial cohorts of early clinical trials often enroll significantly fewer patients than later stage clinical trials or later cohorts of the same clinical trial and may not be as predictive as larger trials. We may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful or come to agreement on other aspects of clinical trial design. Moreover, a clinical trial can fail at any stage of testing. Differences in trial design between early- stage clinical trials and later- stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials. Moreover, clinical data are often

susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their products. A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or to unfavorable safety profiles, notwithstanding promising results in earlier trials. There is typically a high rate of failure of product candidates proceeding through clinical trials. Most product candidates that commence clinical trials are never approved as products and there can be no assurance that any of our future clinical trials will ultimately be successful or support clinical development of our current or any of our future product candidates. We **,** or our collaborators **,** may experience delays in initiating or completing clinical trials. We **,** or our collaborators **,** also may experience numerous unforeseen events during, or as a result of, any future clinical trials that we could conduct that ~~could~~ **40could** delay or prevent our ability to receive marketing approval or commercialize our clinical product candidates or any future product candidates, including: ● regulators, such as the FDA, may place our clinical trials on clinical hold; ● institutional review boards, or IRBs, the FDA or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site; ~~42~~ ● ~~we may experience~~ delays in reaching, or ~~fail~~ **failure** to reach, agreement on acceptable terms with prospective trial sites and prospective CROs the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites; ● clinical trial sites deviating from trial protocol or dropping out of a trial; ● novel therapies, such as gene therapies with less well-characterized safety profiles, may require slower or more staggered early clinical trial enrollment to adequately assess safety data; ● clinical trials of any product candidates may fail to show safety or efficacy, produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs; ● the number of subjects required for clinical trials of any product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate **,** or subjects may drop out of these clinical trials or fail to return for post- treatment follow up at a higher rate than we anticipate; ● our third- party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators; ● we may elect to, or regulators, IRBs, or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants in our trials are being exposed to unacceptable health risks; ● ~~the related~~ expenses of clinical trials of any of our product candidates may be greater than we anticipate; ● the quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be inadequate to initiate or complete a given clinical trial; ● our inability to manufacture sufficient quantities of our product candidates for use in clinical trials; ● reports from clinical testing of other therapies may raise safety or efficacy concerns about our product candidates; ● our failure to establish an appropriate safety profile for a product candidate based on clinical or preclinical data for such product candidate as well as data emerging from other molecules in the same class as our product candidate; and ● the FDA or ex- U. S. regulatory agencies may require us to submit additional data such as long- term toxicology studies or impose other requirements before permitting us to initiate a clinical trial. Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including: the size and nature of the patient population; the number and location of clinical sites we enroll; the proximity of patients to clinical sites; the eligibility and exclusion criteria for the trial; the design of the clinical trial; the inability to obtain and maintain patient consents; the risk that enrolled participants will drop out before completion; and competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs or therapeutic biologics that may be approved for the indications being investigated by us. Furthermore, we expect to rely on our collaborators, CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials, including the patient enrollment process, and we have limited influence over their performance. Additionally, we could encounter delays if treating physicians encounter unresolved ethical issues associated with enrolling patients in future clinical trials of our product candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. For example, treating physicians with eligible patients for our ~~FTD~~ **upliFT- D** trial may instead elect to use alternative treatment approaches from our competitors, if such competitors are to receive regulatory approval in advance of our program, in lieu of enrolling in our clinical trial. We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs of the institutions in which such trials are being conducted, or the FDA or other regulatory authorities, or if a clinical trial is recommended for ~~suspension~~ **41suspension** or termination by the Independent Data Monitoring Committee for such trial. A suspension or termination may be imposed due to a number of factors, including: failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols; inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold; unforeseen safety issues or adverse side effects; failure to demonstrate a benefit from using a product or treatment; failure to establish or achieve clinically meaningful trial endpoints; changes in governmental regulations or administrative actions; or lack of adequate funding to continue ~~43the~~ -- **the** clinical trial. Clinical studies may also be delayed or terminated as a result of ambiguous or negative interim results. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials. Our product development expenses will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do, potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our clinical

development programs may harm our business, financial condition and results of operations significantly. Success in early preclinical studies or clinical trials may not be indicative of results obtained in later preclinical studies and clinical trials. Conducting preclinical testing is a lengthy, time- consuming and expensive process. The length of time of such testing may vary substantially according to the type, complexity and novelty of the program, and often can be several years or more per program. Delays associated with programs for which we are conducting preclinical testing and studies may cause us to incur additional operating expenses. We may experience unexpected or adverse results in our ongoing or future clinical trials. We will be required to demonstrate through adequately designed and executed clinical trials that our product candidates are safe and effective, with a favorable benefit- risk profile, for use in their target indications before we can seek regulatory approvals for their commercial sale. Our ~~initial~~ **current** clinical ~~trials~~ **trial** ~~have started with~~ **for PBFT02 in FTD- GRN patients has** relatively small cohorts ~~before expanding in size in subsequent cohorts~~ **and results experienced to date may not be indicative of future success** . If safety issues arise ~~in an early cohort~~ , we may be delayed or prevented from ~~subsequently~~ expanding into ~~larger~~ **subsequent phases of our** trial ~~cohorts~~ . Earlier gene therapy clinical trials conducted by others also utilized AAV vectors. However, these studies should not be relied upon as evidence that our planned clinical trials will succeed. Trial designs and results from previous trials are not necessarily predictive of our future clinical trial designs or results, and initial positive results we may observe may not be confirmed upon full analysis of the complete trial data. In addition, the positive results we have observed for our product candidates in preclinical animal models may not be predictive of our future clinical trials in humans. Our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development even if they successfully advance through initial clinical trials. Preliminary, topline or interim data from our clinical trials that we or our partners announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data. From time to time, we have made, and may continue to make, public preliminary, topline or interim data from our clinical trials, including preliminary biomarker data. Preliminary or topline data from clinical trials remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary or topline data that were previously made public. Interim data from clinical trials that we may complete are also subject to the risk that one or more of the clinical outcomes may materially change as subject enrollment continues and more data become available. As a result, preliminary, topline and interim data should be viewed with caution until the final data are available. Adverse differences between preliminary, topline or interim data and final data could significantly harm our reputation and business prospects. ~~If~~ **42If** we do not achieve our projected development goals in the time ~~-~~ frames we announce and expect, the commercialization of our products may be delayed. From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, manufacturing and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of preclinical studies and clinical trials, the release of data from such studies and the submission of regulatory filings, including IND submissions. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are, and will be, based on a variety of assumptions. ~~44The~~ ~~-~~ **The** actual timing of these milestones can vary significantly compared to our estimates, in some cases for reasons beyond our control. We may experience numerous unforeseen events during, or as a result of, any future clinical trials that we conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates. Gene therapy is a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval. Currently, only a limited number of gene therapy products have been approved in the United States and in foreign countries. Our current product candidates are based on gene therapy technology and our future success depends on the successful development of this novel therapeutic approach. The regulatory requirements that govern any novel gene therapy product candidates we develop are not entirely clear and are subject to change. The clinical study requirements of the FDA and ex- U. S. regulatory agencies 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 potential products. The regulatory approval process for novel product candidates such as ours may be more expensive and take longer than for other, better known or extensively studied product candidates. Further, as we are developing novel treatments for diseases in which there is little clinical experience with new endpoints and methodologies, there is heightened risk that the FDA or comparable foreign regulatory bodies may not consider the clinical trial endpoints to provide clinically meaningful results, and the resulting clinical data and results may be more difficult to analyze. To date, only a limited number of gene therapy products have been approved in the United States and foreign countries, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States or other jurisdictions. Further, approvals by ex- U. S. regulatory agency may not be indicative of what the FDA may require for approval, or vice versa. Our product candidates may cause undesirable and unforeseen side effects, which could delay or prevent their advancement into clinical trials or regulatory approval, limit the commercial potential or result in significant negative consequences. While new AAV vectors have been developed to reduce side effects previously reported in third- party gene therapy treatments, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. For example, **two patients** in our ~~clinical study~~ **upliFT- D trial have experienced a total of three serious adverse events, all of which were asymptomatic and likely consistent with an immune response. As a result of the immune response observed in the first patient dosed, who received a low initial level of immunosuppression (60 mg oral prednisone daily** for ~~PBKR03~~ **60 days)** , ~~for which, in order to reduce operating expenses,~~ we **amended the protocol to increase the steroid regimen. Subsequent to the** ~~have stopped further clinical development and are exploring out- licensing opportunities for this asset, a patient experienced a grade 4~~ serious adverse event ~~of acute communicating hydrocephalus~~ **experienced by the seventh patient, the Company introduced a new dose (Dose 2),**

which is half the dose used in patients one through seven (Dose 1), and plans to study Dose 2 for all remaining patients in Cohort 2 . Additional possible adverse side effects ~~that~~ could occur **that may require changes to the protocol in the future. Further** ~~with treatment with gene therapy products include an immunologic reaction early after administration which~~ , ~~while not necessarily~~ adverse **side effects** ~~to the patient' s health,~~ could substantially limit the effectiveness of the treatment. For example, in previous third- party clinical trials involving AAV vectors for gene therapy, some subjects experienced the development of a T- cell immune response, whereby after the vector is within the target cells, the cellular immune response system triggers the removal of transduced cells by activated T- cells. Other recent clinical trials involving high doses of AAV vectors have also resulted in liver damage and death. Further, following administration of any AAV vector, patients are likely to develop neutralizing antibodies specific to the vector administered. Other preclinical studies have suggested that high dosages of AAV administration may result in toxicity due to degeneration of the dorsal root ganglia. Preliminary results of our NHP toxicology studies for our ~~PBGM01 and~~ PBFT02 ~~product~~ **43product** ~~candidates~~ **candidate** have demonstrated trigeminal ganglia and dorsal root ganglia toxicity. Based on these results, and if our vectors demonstrate a similar effect in other programs, we may decide or be required to perform additional preclinical studies or to halt or delay further clinical development of our product candidates. In addition to side effects caused by the product candidate, the administration process or related procedures also can cause adverse side effects. Each of our clinical product candidates are expected to utilize ICM administration. While this method of administration has been available for decades, its use for therapies is relatively new, no therapies are currently approved using ICM administration, and it may be perceived as having greater risk than more common methods of administration, such as intravenous injection. If any such adverse events occur, our clinical trials could be suspended or terminated. If we cannot demonstrate that any adverse events were not caused by the drug or administration process or ~~45related~~ **related** procedures, the FDA or ex- U. S. regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to not initiate, delay, suspend or terminate any future 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. Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategies, or REMS, to ensure that the benefits of the product outweigh its risks, which 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. Furthermore, 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 in the labeling; ● 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 occurrences may harm our business, financial condition and prospects significantly. Adverse public perception of genetic medicines may negatively impact regulatory approval of, and / or demand for, our potential products. Regulatory approval of and / or demand for our potential products will depend in part on public acceptance of the use of genetic medicine for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that genetic medicines are unsafe, unethical or immoral, and consequently, our products may not gain the acceptance of the public or the medical community. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, their patients being willing to receive, and third- party payors being willing to cover and reimburse for ~~,~~treatments that involve the use of product candidates we may develop. There have been several significant adverse side effects reported in genetic medicine treatments in the past. For example, in 1999, there was public backlash against gene therapy following the death of a clinical trial subject in a gene therapy clinical trial that utilized an adenovirus vector. It was later discovered that adenoviruses could generate an extreme immune system reaction that can be life threatening. Dr. **James** Wilson, ~~our Chief~~ **who also serves as a consultant to us as a** Scientific Advisor, was a co-investigator of the 1999 trial while he was Director of the Institute for Human Gene Therapy of Penn. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy by us or our competitors, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception and potential regulatory delays in the clinical testing or approval of our product candidates. ~~As~~ **44As** an organization, we have limited experience designing and implementing clinical trials and we have never conducted pivotal clinical trials. Failure to adequately design a trial, or incorrect assumptions about the design of the trial, could adversely affect the ability to initiate the trial, enroll patients, complete the trial, or obtain regulatory approval on the basis of the trial results, as well as lead to increased or unexpected costs. The design and implementation of clinical trials is a complex process. As an organization, we have limited experience designing and implementing clinical trials, and we may not successfully or cost effectively design and implement clinical trials that achieve our desired clinical endpoints efficiently, or at all. A clinical trial that is not well designed may delay or even prevent initiation of the trial, can lead to increased difficulty in enrolling patients, may make it more difficult to obtain regulatory approval for the product candidate on the basis of the study results, or, even if a product ~~46candidate~~ **candidate** is approved, could make it more difficult to commercialize the product successfully or obtain reimbursement from third- party payors. Additionally, a trial that is not well designed could be inefficient or more expensive than it otherwise would have been, or we may incorrectly estimate the related expenses to implement the clinical trial, which could lead to a shortfall in funding. Certain disorders we seek to treat have low incidence and prevalence, and it may be difficult to identify patients with these disorders, which may lead to delays in enrollment for our trials or slower commercial revenue if approved. Genetically defined disorders generally, and especially those for which certain of our current product candidates are targeted, have low

incidence and prevalence. For example, we estimate the prevalence of FTD- GRN deficiency in the United States and Europe is approximately 18, 000. This could be a significant obstacle to the timely recruitment and enrollment of a sufficient number of eligible patients into our trial. Further, we expect to rely in part on our relationships with patient advocacy groups to assist in identifying eligible patients, and any deterioration of those relationships could impede our ability to successfully enroll patients. Patient enrollment may be affected by other factors including: ● the severity of the disease under investigation; ● design of the study protocol; ● the eligibility criteria for the trial; ● the perceived risks, benefits and convenience of administration of the product candidate being studied; ● our efforts to facilitate timely enrollment in clinical trials; ● the availability of other clinical trials being conducted for the same indication; ● the patient referral practices of physicians; and ● the proximity and availability of clinical trial sites to prospective patients. Our inability to enroll a sufficient number of patients with these diseases for our planned clinical trials, including FTD- GRN, would result in significant delays and could require us to not initiate or abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. Additionally, our projections of the number of people who have these disorders, including FTD- GRN, are based on estimates, including third- party analyses commissioned by us. The total addressable market opportunity for our product candidates will ultimately depend upon, among other things, the final approved product labeling for each of our product candidates, if our product candidates are approved for sale in our target indications, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients globally may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business. Our products may potentially be dosed on a one- time basis, which means that patients who enroll in our clinical trials may not be eligible to receive our products on a commercial basis if they are approved, leading to lower revenue potential. ~~Even~~ **45Even** if we complete the necessary clinical trials, we cannot predict when, or if, we will receive regulatory approval to commercialize a product candidate and the approval may be for a more narrow indication than we seek. Prior to commercialization, our product candidates must be approved by the FDA pursuant to a **Biologics License Application, or** BLA **,** in the United States and by similar ex- U. S. regulatory authorities. The process of obtaining marketing approvals, both in the United States and abroad, is expensive and takes many years, 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. 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. Our company does not have experience in submitting and supporting the applications necessary to gain marketing approvals. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be ~~47only --~~ **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. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Approval of our product candidates may be delayed or refused for many reasons, including the following: ● the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials, including the methods for collecting and analyzing data, the statistical analysis plan, and the lack of a concurrent control arm or a decision to use external or historical controls; ● the FDA or comparable foreign regulatory authorities may not agree that the efficacy endpoints used in our clinical trials are appropriate to establish clinical benefit in the intended populations; ● we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that our product candidates are safe and effective for any of their proposed indications; ● development of products for ultra rare diseases may involve the use of natural history data as an external control. We may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that the control arm (s) are adequate to establish the safety and / or effectiveness of our product candidates; ● the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval; ● we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities a durable response to our product candidates; ● we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks; ● the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical programs or clinical trials; ● the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a BLA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere; ● the facilities of the third- party manufacturers with which we contract may not be adequate to support approval of our product candidates; ● the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval; and ● even if our product candidates meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non- approval or restrictions on approval. In addition, we may experience delays or ~~rejections~~ **46rejections** based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials and the review process. **In addition, three decisions from the U. S. Supreme Court in July 2024 may lead to an increase in litigation against regulatory agencies that could create uncertainty and thus negatively impact**

our business. The first decision overturned established precedent that required courts to defer to regulatory agencies' interpretations of ambiguous statutory language. The second decision overturned regulatory agencies' ability to impose civil penalties in administrative proceedings. The third decision extended the statute of limitations within which entities may challenge agency actions. These cases may result in increased litigation by industry against regulatory agencies and impact how such agencies choose to pursue enforcement and compliance actions. However, the specific, lasting effects of these decisions, which may vary within different judicial districts and circuits, is unknown. We also cannot predict the extent to which FDA and SEC regulations, policies, and decisions may become subject to increasing legal challenges, delays, and changes. Regulatory authorities also may approve a product candidate for more limited indications than requested or they may impose significant limitations in the form of narrow indications, warnings or REMS. These regulatory authorities may require precautions or contra indications with respect to conditions of use or they may grant approval subject to the performance of costly post- marketing clinical trials. In addition, regulatory authorities may not approve the product labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially and adversely affect our business, financial condition, results of operations and prospects. Further, the regulatory authorities may require concurrent approval of a companion diagnostic device. For our product candidates, it may be necessary to use FDA- cleared or FDA-approved diagnostic tests to diagnose patients or to assure ~~48the~~ -- **the** safe and effective use of product candidates in trial subjects. The FDA refers to such tests as in vitro companion diagnostic devices. The FDA has issued guidance describing the agency' s current thinking about the development and regulation of in vitro companion diagnostic devices. The final guidance articulates a policy position that, when an in vitro diagnostic device is essential to the safe and effective use of a therapeutic product, the FDA generally will require approval or clearance of the diagnostic device at the same time that the FDA approves the therapeutic product. At this point, it is unclear how the FDA will apply this policy to our current or future gene therapy product candidates. Should the FDA deem genetic tests used for diagnosing patients for our therapies to be in vitro companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates. The FDA and ex- U. S. regulatory agencies have demonstrated caution in their regulation of gene therapy treatments. Ethical and legal concerns about gene therapy and genetic testing may result in additional regulations or restrictions on the development and commercialization of our product candidates, which may be difficult to predict. The FDA and ex- U. S. regulatory agencies at both the federal and state level in the United States, U. S. congressional committees, and foreign governments, have expressed interest in further regulating the biotechnology industry, including gene therapy and genetic testing. Any such further regulation may delay or prevent commercialization of some or all of our product candidates. Regulatory requirements in the United States and abroad governing gene therapy products have changed frequently and may continue to change in the future. In addition to the FDA, the Institutional Biosafety Committee and IRB of each institution at which we conduct our planned clinical trials, would need to review the proposed clinical trial to assess the safety of the trial. Within the FDA, the Office of **Therapeutic Products** ~~Tissues and Advanced Therapies~~ , within the Center for Biologics Evaluation and Research, or CBER, consolidates the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee advises CBER on its review. Adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. 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 or trials, increase our development costs, lead to ~~changes~~ **47changes** in regulatory positions and interpretations, delay or prevent approval and commercialization of our 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. If we fail to do so, we may be required to delay or discontinue development of such 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 an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all. ~~Changes in funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products 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. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.~~ Disruptions at the FDA ~~and~~ **or** other ~~agencies~~ **comparable foreign regulatory authorities** may also slow the time necessary for new ~~drugs~~ **products** to be reviewed and / or approved ~~by necessary government agencies~~ , which would adversely affect our business. **In addition, there is substantial uncertainty regarding the new Administration' s initiatives and how these might impact the FDA, its implementation of laws, regulations, policies and guidance and its personnel. These initiatives could prevent, limit or delay development and regulatory approval of our product candidates, which would adversely affect our business. Disruptions at the FDA or other comparable foreign regulatory authorities may also slow the time necessary for new products to be reviewed and / or approved, which would adversely affect our business. Changes in FDA staffing could result in delays in the FDA' s responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Similar consequences would also result in the event of another significant shutdown of the federal government.** For example, **in 2024** ~~over the last several years~~ , ~~including for 35 days beginning~~ **the U. S. government was** on ~~December 22, 2018,~~ the ~~U. S. government~~ **verge of a shutdown and** has **previously** shut down several times **,** and certain regulatory agencies,

such as the FDA, ~~have~~ had to furlough critical ~~FDA~~ employees and stop ~~important~~ **critical** activities. If a prolonged government shutdown occurs, **or if geopolitical or global health concerns prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities,** it could significantly impact the ability of the FDA **or other regulatory authorities** to timely review and process our regulatory submissions, which could have a material adverse effect on our business. **Further, future government shutdowns or delays could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations. If the FDA is constrained in its ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted. In addition, FDA- regulated industries, such as ours, face substantial uncertainty in regard to the regulatory environment we will face as we proceed with research and development efforts following the change of the U. S. Government Administration in January 2025. Some of these efforts have manifested to date in the form of personnel measures that could impact the FDA' s ability to hire and retain key personnel, which could result in delays or limitations on our ability to obtain guidance from the FDA on our product candidates in development and obtain the requisite regulatory approvals in the future. There remains general uncertainty regarding future activities. The new Administration could issue or promulgate executive orders, regulations, policies or guidance that adversely affect us or create a more challenging or costly environment to pursue the development of new therapeutic products. Alternatively, state governments may attempt to address or react to changes at the federal level with changes to their own regulatory frameworks in a manner that is adverse to our operations. If we become negatively impacted by future governmental orders, regulations, policies or guidance as a result of the new Administration, there could be a material adverse effect on us and our business.** ~~49Failure~~ -- **Failure** to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad and will limit our ability to realize their full market potential. In order to eventually market any of our product candidates in any particular foreign jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a jurisdiction by jurisdiction basis regarding safety and efficacy. Approval by the FDA in the United States, if obtained, does not ensure approval by regulatory authorities in other countries or jurisdictions. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time- consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in ~~those~~ **48those** countries. The foreign regulatory approval process involves all of the risks associated with FDA approval. 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 **, or EU** . 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. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets and expect to rely on third- party consultants. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products will be unrealized. We may not be successful in our efforts to build a pipeline of additional product candidates. Our business model is centered on developing therapies for patients with CNS disorders by establishing focused selection criteria to select, develop and advance product candidates that we believe will have a ~~high~~ **higher** probability of technical and regulatory success through development into commercialization. We may not be able to continue to identify and develop new product candidates in addition to the pipeline of product candidates that we have established through our collaboration with GTP **. As a result of the Outlicense Transaction Agreements, we no longer have a collaboration with GTP and instead have a collaboration with Gemma** . Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development. For example, they may be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our approach, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price. Risks Related to Our Reliance on Third PartiesWe currently rely on our collaboration with **Gemma** ~~GTP,~~ for many aspects of our preclinical research and development programs, including for discovering, preclinically developing and conducting IND- enabling studies for our ~~clinical~~ **preclinical** product candidates and our near- term future pipeline of product candidates. Failure or delay of ~~GTP~~ **Gemma** to fulfill all or part of its obligations to us under the agreement, a breakdown in collaboration between the parties or a complete or partial loss of this relationship could materially harm our business. **As part** ~~Our collaboration with GTP has been critical to the development of our current clinical pipeline. We~~ **the Outlicense Transaction Agreements, we** entered into **the Gemma** ~~an amended and restated Research,~~ Collaboration ~~& License~~ Agreement ~~in May 2020, as subsequently amended, or the Penn Agreement,~~ with ~~GTP~~ **Gemma** to discover and develop certain AAV vector **-** based therapeutics, and the products developed under such collaboration currently represent all of our product pipeline and research programs. We currently rely on ~~GTP~~ **Gemma** for preclinical research and development capabilities for new product candidates. Pursuant to the ~~Penn~~ **Gemma Collaboration** Agreement, ~~GTP~~ **Gemma** is responsible for discovery, preclinical development activities, including IND- enabling non- clinical studies and research grade manufacturing ~~,~~ and other collaborative activities set forth in the plan for the funded research. Either party has the right in certain circumstances to terminate the collaboration pursuant to the terms of the ~~Penn~~ **Gemma Collaboration** Agreement. If ~~GTP~~ **Gemma** delays or fails to perform its obligations under the ~~Penn~~ **Gemma Collaboration** Agreement,

disagrees with our interpretation of the terms of the ~~50collaboration~~ **collaboration** or our discovery plan or terminates our existing agreement, our future pipeline of product candidates could be significantly adversely affected and our prospects will be materially harmed. The term of the research funding portion of the ~~Penn~~ **Gemma Collaboration** Agreement, under which we have the ability to acquire exclusive rights to additional gene therapy products for CNS indications, expires in ~~August~~ **July** ~~2026~~ **2029** ~~. In addition, the discovery program, under which we have rights to new technologies for our product candidates is currently also set to expire in August 2026. The term of the exploratory research program in large indications expires in August 2024~~. If we seek to extend or alter the terms of our collaboration, we will need to negotiate a new or amended agreement, which may not be available to us on equally favorable terms, if at all. ~~GTP~~ **Gemma** has also entered into collaborations with third parties, including certain of our competitors, addressing targets and disease indications outside the scope of our collaboration. As a result, ~~GTP~~ **Gemma** may have competing interests with respect to their priorities and resources. We may have disagreements with ~~GTP~~ **Gemma** with respect to the interpretation of the ~~Penn~~ **Gemma Collaboration** Agreement, use of resources or otherwise that could cause our relationship with ~~GTP~~ **Gemma** to deteriorate. As a result, ~~GTP~~ **Gemma** may reduce their focus on, and resources allocated to, our programs, potentially delaying or terminating our ability to advance product candidates ~~through~~ **49through** preclinical studies. **If** ~~Additionally, if~~ Dr. Wilson were to leave ~~GTP~~ **Gemma** or to otherwise no longer be meaningfully involved with us, our preclinical research and development capabilities may be substantially reduced. **Additionally, as a newly formed company, Gemma could face operational and financial challenges that could impact its ability to execute under the Gemma Collaboration Agreement.** Further, under the Penn **License** Agreement **and the Gemma Collaboration Agreement**, ~~GTP is~~ **Gemma and Penn are** primarily responsible for prosecuting and maintaining our licensed intellectual property, and ~~it~~ **either of them** may fail to properly prosecute, maintain or defend such intellectual property. In such event, if we are unable to otherwise maintain or defend such intellectual property, we could face the potential invalidation of the intellectual property or be subjected to litigation or arbitration, any of which would be time- consuming and expensive. To enforce the licensed intellectual property rights under the Penn **License Agreement or the Gemma Collaboration** Agreement, we will need to coordinate with ~~GTP~~ **Penn and Gemma, respectively**, which could slow down or hamper our ability to enforce our licensed intellectual property rights. In such **an** event, we could face increased competition that could materially and adversely affect our business. We rely on third parties to conduct our preclinical studies and clinical trials and rely on them to perform other tasks for us. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed. Although we have recruited a team that has experience with clinical trials, as a company **,** we have limited experience in conducting clinical trials. Moreover, we currently rely on third- parties, ~~currently~~ **now** primarily ~~GTP~~ **Gemma**, for our discovery and certain of our preclinical research **,** and will continue to rely upon medical institutions, clinical investigators, and CROs to conduct clinical trials for our product candidates. We expect to rely heavily on these parties for execution of preclinical and clinical trials for our product candidates and control only certain aspects of their activities. If these parties reduce the levels of efforts and resources to our product candidate activities, prioritize work with a competitor of ours or if a dispute were to arise between us and these parties, they may not meet our expected deadlines or provide us with sufficient materials for our regulatory filings. Nevertheless, we will be responsible for ensuring that each of our preclinical and clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards and our reliance on CROs will not relieve us of our regulatory responsibilities. For any violations of laws and regulations during the conduct of our preclinical studies and clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution. We, ~~GTP~~ **Gemma**, and our CROs will be required to comply with regulations, including cGCPs for conducting, monitoring, recording and reporting the results of preclinical and clinical trials to ensure that the data and results are scientifically credible and accurate and that the trial patients are adequately informed of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any drugs in clinical development. The FDA enforces cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators, and trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our future clinical trials will comply with cGCPs. In addition, our clinical trials must be conducted with product candidates produced in accordance with the requirements in the current Good ~~51Manufacturing~~ **Manufacturing** Practices, or cGMP regulations. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action. Although we currently design and intend to continue designing our planned clinical trials for our product candidates, for the foreseeable future CROs will conduct all of our planned clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future preclinical studies and clinical trials will also result in less day- to- day control over the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. ~~If~~ **50If** any of our relationships with these third- party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any preclinical studies or clinical trials with which such CROs are associated with may be extended, delayed or terminated. In such cases, 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

in the subject indication could be harmed, our costs could increase and our ability to generate revenue could be delayed. We rely on third parties to conduct our clinical trials. If those third parties do not perform as contractually required, fail to satisfy legal or regulatory requirements, miss expected deadlines or terminate the relationship, our development program could be delayed with potentially material and adverse effects on our business, financial condition, results of operations and prospects. We rely on third- party clinical investigators, CROs, clinical data management organizations and consultants to assist or provide the design, conduct, supervision and monitoring of clinical trials of our product candidates. Because we rely and intend to rely on these third parties and will not have the ability to conduct all clinical trials independently, we will have less control over the timing, quality and other aspects of clinical trials than we would have had we conducted them on our own. These investigators, CROs and consultants will not be our employees and we will have limited control over the amount of time and resources that they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw time and resources from our programs. The third parties with which we may contract might not be diligent, careful or timely in conducting our clinical trials, resulting in the clinical trials being delayed or unsuccessful. If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we will be responsible for ensuring that each of our preclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial as well as applicable legal and regulatory requirements. The FDA generally requires preclinical studies to be conducted in accordance with GLPs and clinical trials to be conducted in accordance with cGCPs, including for designing, conducting, recording and reporting the results of preclinical studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control will not relieve us of these responsibilities and requirements. Any adverse development or delay in our preclinical studies or clinical trials as a result of our reliance on third parties could have a material and adverse effect on our business, financial condition, results of operations and prospects. If any of our relationships with these third- party CROs or others terminate, we may not be able to enter into alternative arrangements or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially adversely impact our ability to meet our desired clinical development timelines. ~~52We~~ **We have outlicensed our lysosomal pediatric products to Gemma, a genetic medicines company, and we** may in the future enter into collaborations with other third parties for the discovery, development and commercialization of our product candidates. If any of our current or future collaborators cease development efforts under our collaboration agreements, or if any of those agreements are terminated, these collaborations may fail to lead to commercial products and we may never receive milestone payments or future royalties under these agreements. ~~We~~ **Gemma is a newly- formed company with a limited history of operations. If Gemma is not successful in continuing the development and commercialization of the lysosomal pediatric products that we have licensed to them, we will not receive any downstream economic benefit and the products will revert back to us. 51We** may in the future enter into third- party collaborations for research, development and commercialization of other therapeutic technologies or product candidates. Biotechnology companies are our likely future collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements. With **Gemma and** any future collaboration agreements, we expect to have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Moreover, our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. Our **current and** potential future collaborations involving our product candidates may pose the following risks to us: ● collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations; ● collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on preclinical studies or clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities; ● collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing; ● collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; ● collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products; ● collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to litigation or potential liability; ● collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation, indemnification obligations and potential liability; ● disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources; collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates; ● if a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated; and ● collaboration agreements may restrict our right to independently pursue new product candidates. As a result of the foregoing, **our current and** any future collaboration agreements may not lead to development or commercialization of our product candidates in the most efficient manner or at all.

If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated. Any failure to successfully develop or commercialize our product candidates pursuant to our current or any future collaboration agreements could have a material and adverse effect on our business, financial condition, results of operations and prospects. ~~53Moreover~~ -- **Moreover**, to the extent that any of our existing or future collaborators were to terminate a collaboration agreement, we may be forced to independently develop our product candidates and research programs, including funding preclinical studies or clinical trials, assuming marketing and distribution costs and maintaining and defending intellectual property rights, or, in certain instances, abandon product candidates altogether, any of which could result in a change to our business plan and have a material adverse effect on our business, financial condition, results of operations and prospects. ~~We~~ **52We** may not be successful in finding additional collaborators for continuing development of certain of our product candidates or successfully commercializing or competing in the market for certain indications. We may decide to pursue collaborations with additional pharmaceutical and biotechnology companies for the development and potential commercialization of some of our product candidates ~~. In particular, we recently announced that we are pursuing potential out- licensing opportunities for our pediatric portfolio of clinical programs including GM1, Krabbe, and MLD~~. We face significant competition in seeking appropriate collaborators. Any new collaboration may be on terms that are not optimal for us, and we may not be able to maintain any new collaboration if, for example, development or approval of a product candidate is delayed, sales of an approved product candidate do not meet expectations or the collaborator terminates the collaboration. In addition, a significant number of recent business combinations among large pharmaceutical companies has resulted in a reduced number of potential future collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator' s evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA 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 drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us. We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time- consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue. We may have conflicts with our collaborators that could delay or prevent the development or commercialization of our product candidates. We may have conflicts with our collaborators, including ~~GTP~~ **Penn and Gemma**, such as conflicts concerning the interpretation of preclinical or clinical data, the achievement of milestones, the interpretation of contractual obligations, payments for services, development obligations or the ownership of intellectual property developed during our collaboration. If any conflicts arise with any of our collaborators, such collaborator may act in a manner that is adverse to our best interests. Any such disagreement could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating revenues: unwillingness on the part of a collaborator to pay us milestone payments or royalties we believe are due to us under a collaboration, which could require us to raise additional capital; uncertainty regarding ownership of intellectual property ~~54rights~~ -- **rights** arising from our collaborative activities, which could prevent us from entering into additional collaborations; unwillingness by the collaborator to cooperate in the development or manufacture of the product, including providing us with product data or materials; unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities; initiating of litigation or alternative dispute resolution options by either party to resolve the dispute; or attempts by either party to terminate the relevant agreement. ~~We~~ **53We** may in the future seek to engage in strategic transactions to acquire or in- license new products, product candidates or technologies. If we are unable to successfully complete, or realize the benefits from, such transactions it may adversely affect our ability to develop and commercialize product candidates, impact our cash position, increase our expenses and present significant distractions to our management. From time to time, we may consider strategic transactions, such as additional collaborations, acquisitions of companies, asset purchases, joint ventures and in- licensing of new products, product candidates or technologies that we believe will complement or augment our existing business. If we acquire assets with promising markets or technologies, we may not be able to realize the benefit of acquiring such assets if we are not able to successfully integrate them with our existing technologies. We may encounter numerous difficulties in developing, testing, manufacturing and marketing any new products resulting from a strategic acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that following any such strategic transaction, we will achieve the expected synergies to justify the transaction. For example, such transactions may require us to incur non- recurring or other charges, increase our near- and long- term expenditures and pose

significant integration or implementation challenges or disrupt our management or business. These transactions would entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of our business and diversion of our management' s time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected acquisition or integration costs, write- downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the transaction or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and would have a material and adverse effect on our business, financial condition, results of operations and prospects. Conversely, any failure to enter any strategic transaction that would be beneficial to us could delay the development and potential commercialization of our product candidates and have a negative impact on the competitiveness of any product candidate that reaches market. Risks Related to ManufacturingGene therapies are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in our development or commercialization programs or otherwise harm our business. We currently rely on third parties to develop, manufacture and test clinical supplies of our product candidates, including the materials used to administer our product candidates. For our initial clinical trials, we rely on the manufacturing facility of Catalent Maryland, a unit of Catalent, Inc. **acquired by Novo Holdings A / S** , or Catalent, for supply of our product candidates. We have limited experience as a company in developing manufacturing facilities. If or when we decide to construct our own manufacturing facility for long- term commercial market supply, we may face delays in building out a plant, constructing new facilities, transferring technology to the facilities or hiring experts to staff and operate the facilities and, accordingly, our production capacity could be limited. We **use** ~~have established internal testing operations supporting our preclinical and clinical manufacturing in addition to using~~ external contract testing labs and ~~established~~ analytical development and process development ~~capabilities~~ **services** to support our pipeline. The manufacturing processes used to produce our product candidates are complex, novel and have not been validated for commercial use. Many factors could cause ~~55production~~ -- **production** interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers. Our product candidates require processing steps that are more complex than those required for most small molecule drugs. Moreover, unlike small molecules, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product is consistent from lot- to- lot or will perform in the intended manner. **For example, we have recently developed a potency 54assay for release of PBFT02 for late- stage clinical studies and commercialization. While we have received initial positive feedback from the FDA on the suitability of our proposed potency assay, there can be no assurance that this assay will be approved by the FDA or ensure product potency.** Accordingly, we employ multiple steps to control the manufacturing process to assure that the process works consistently and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, low lot yields, product recalls, product liability claims or insufficient inventory. As a result, we may encounter problems achieving adequate quantities and quality of clinical- grade materials that meet the FDA or other applicable standards or specifications with consistent and acceptable production yields and costs. In addition, the FDA and ex- U. S. regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA or ex- U. S. regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures, low lot yields or product recalls. Lot failures, low lot yields or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. We, or our third- party collaborators, also may encounter problems hiring and retaining the experienced scientific, quality- control and manufacturing personnel needed to operate our manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements. Any problems in our, or our third- party collaborators', manufacturing process or facilities could result in delays in our planned clinical trials and increased costs, and could make us a less attractive collaborator for potential partners, including larger biotechnology companies and academic research institutions, which could limit our access to additional attractive development programs. It could also require us to find alternative manufacturing processes, which may be unavailable to us on attractive terms, or at all. Problems in our manufacturing process could restrict our ability to meet potential future market demand for our products. Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay. As product candidates proceed through preclinical studies to late- stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue. ~~56We~~ **We** currently rely and expect to continue to rely on third- party manufacturers **and labs** to produce **and test** clinical supply of our product candidates, and we have not entered into

binding agreements with any such ~~manufacturers~~ **partners** to support commercialization **. Furthermore, these service providers lack experience in producing our product candidates at commercial scale. As a result, they may not obtain the necessary regulatory approvals or may not be able to produce and test our product candidates at the required quality, quantity, locations, and timelines needed for successful commercialization. We currently rely, and expect to continue to rely, on third parties for the production of our preclinical study and planned clinical trial materials, including the materials used to administer our product candidate and, therefore, we can control only certain aspects of their activities** . The competition for gene therapy contract development, manufacturing and testing ~~services is intense. Additionally, these manufacturers do not have experience producing our product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our product candidates at the quality, quantities, locations and timing needed to support commercialization. While we are in the process of establishing manufacturing capability for certain clinical manufacturing activities, we do not currently plan to independently manufacture most of the material for our planned clinical programs. We currently rely, and expect to continue to rely, on third parties for the production of our preclinical study and planned clinical trial materials, including the materials used to administer our product candidates and, therefore, we can control only certain aspects of their activities. The competition for gene therapy contract development, manufacturing and testing~~ is intense. Reliance on third- party manufacturers **and analytical testing labs** may expose us to different risks than if we were to manufacture **and test** product candidates ourselves, including but not limited to potential competition from ~~other~~ **55other** genetic biotechnology companies for the use of such third- party ~~manufacturers~~ **services** . For example, we currently rely on Catalent to manufacture our clinical supply ~~. However, following the recently announced acquisition of Catalent by Novo Holdings A / S, we may face delays or other risks to our manufacturing process depending on any changes implemented as result of such transaction~~ . While we have secured an agreement with Catalent to manufacture clinical supply of our product ~~candidates~~ **candidate, we may not be able to secure suifficient capacity to meet our future clinical requirements for clinical supply. Further** , we have not yet secured manufacturing **and analytical testing** capabilities for commercial quantities of our product ~~candidates~~ **candidate** ~~. To date, while we have a collaboration agreement with Catalent, we have only entered into agreements with such manufacturer to support our clinical studies~~ . We may be unable to negotiate binding agreements with ~~the manufacturers~~ **external partners** to support our potential commercialization activities at commercially reasonable terms. In addition, ~~under our current agreements with Catalent, (i) we no longer have exclusive access to the dedicated clean room suite and may not be able to secure future capacity or to meet our requirements for future clinical and commercial supply and (ii)~~ we have an exclusive obligation ~~to~~ **for commercial** manufacture **of** certain products with Catalent and therefore we may be unable to work with other third- party manufacturers. As a result, we may be unable to continue to develop and commercialize our products or product ~~candidates~~ **candidate** . Before any of our third- party ~~manufacturers~~ **partners** and suppliers can begin to commercially manufacture our product candidates, including the materials used to administer our product candidates, they must demonstrate to regulatory authorities that the planned chemistry, manufacturing and controls for our gene therapy product candidates meet certain requirements. Manufacturing of product candidates for clinical and commercial purposes must comply with the cGMP and applicable ex- U. S. regulatory requirements. The cGMP requirements govern quality control and documentation policies and procedures. Complying with cGMP and ex- U. S. regulatory requirements will require that we expend time, money and effort in production, recordkeeping and quality control to assure that our product candidates meet applicable specifications and other requirements. Our third- party manufacturers' **and analytical testing labs** also must demonstrate to the FDA and ex- U. S. regulators that they can make **or test** the product candidate in accordance with the cGMP requirements as part of a pre- approval inspection prior to FDA or similar ex- U. S. regulatory approval of the product candidate. Failure to pass a pre- approval inspection might significantly delay our ability to begin trials in the respective jurisdiction and FDA and ex- U. S. regulatory approval of our product candidates. If any of our third- party manufacturers **or testing labs** fail to comply with these requirements, we would be subject to possible regulatory action, which could limit the jurisdictions in which we are permitted to sell our products. As a result, our business, financial condition and results of operations may be materially harmed. In addition, our third- party manufacturers **or testing labs** may fail to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third- party ~~manufacturers~~ **partners** , to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, 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. Even if our third- party ~~manufacturers~~ **partners** comply with applicable regulatory requirements, we cannot assure ~~you~~ that they will be able to successfully manufacture **and test** additional product candidates at a larger scale in a timely or economical ~~57manner~~ **manner** , or at all. If they are unable to successfully increase our manufacturing scale or capacity, the development, testing, and clinical trials of our product candidates may be delayed or infeasible, and regulatory approval or commercial launch of any resulting product may be delayed or not obtained, which could significantly harm our business. Our third- party manufacturers and suppliers use biological materials and may use hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time- consuming or costly. Our third- party manufacturers and suppliers may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety or the environment. The operations of our third- party manufacturers and suppliers also produce hazardous waste products. Federal, state, and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in

the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended. ~~Any~~ **56Any** contamination in our third parties' manufacturing process, shortages of raw materials, labor or reagents or failure of any of our key suppliers to deliver necessary components of our platform 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 materially adversely affect our or our third-party vendor' s ability to produce our gene therapies on schedule and could therefore harm our results of operations and cause reputational damage. The raw materials required in our third- party vendors **'** manufacturing processes are derived from biological sources. We cannot assure that our third- party vendors have ~~,~~or will be able to obtain on commercially reasonable terms, or at all, sufficient rights to these materials derived from biological sources. Such raw materials are difficult to procure and may also 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 clinical and commercial manufacturing of our product candidates, which could materially and adversely affect our operating results and development timelines. We rely on third- party suppliers for the supply and manufacture of certain components of our technology. Should our ability to procure these material components from our suppliers be compromised, our ability to continuously operate would be impaired until an alternative supplier is sourced, qualified and tested, which could limit our ability to produce a clinical and commercial supply of our product candidates and harm our business. We depend on third- party suppliers for materials used in the manufacture of our product candidates, and the loss of these third- party suppliers or their inability to supply us with adequate materials could harm our business. We rely on third- party suppliers for certain materials and components required for the production of our product candidates, including the materials used to administer our product candidates. Our dependence on these third- party suppliers and the challenges we may face in obtaining adequate supplies of materials involve several risks, including limited control over pricing, availability, and quality and delivery schedules. There is substantial demand and limited supply for certain of the raw materials used to manufacture gene therapy products. As a small company, our negotiation leverage is limited and we are likely to get lower priority than our competitors that are larger than we are. We cannot be certain that our suppliers will continue to provide us with the quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements. Any supply interruption in limited or sole sourced raw materials could materially harm our ability to manufacture our product candidates until a new source of supply, if any, could be identified and qualified. We may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and ~~58potential~~ -- **potential** commercialization of our product candidates, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business. Risks Related to CommercializationWe 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 or technologies 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 biotechnology and pharmaceutical industries, including the genetic medicines field, are characterized by rapidly changing technologies, competition and a strong emphasis on intellectual property. We are aware of several companies focused on developing gene therapies in various indications as well as several companies addressing methods for modifying genes and regulating gene expression. We may also face competition from large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions. For the treatment of FTD, there are no approved disease- modifying therapies. We consider our most direct competitors with respect to PBFT02 for the treatment of FTD- GRN to be **Prevail Therapeutics Inc. (part of Eli Lilly & Co), which is 57conducting a Phase 1 / 2 clinical trial for an ICM administered gene therapy treatment for FTD- GRN and AviadoBio Ltd, which is conducting a Phase 1 / 2 intrathalamic gene therapy trial in patients with FTD- GRN. AviadoBio Ltd entered into an exclusive option and licensing agreement with Astellas in October 2024.** Alector, Inc. (partnered with ~~GlaxoSmithKline~~ **GSK plc**) ~~, which~~ is conducting a Phase 3 clinical trial with a humanized anti- human sortilin monoclonal antibody for FTD- GRN ~~, and Prevail Therapeutics Inc. (now part of Eli Lilly & Co), which is conducting a Phase 1 / 2 clinical trial for a gene therapy treatment for FTD- GRN. AviadoBio began enrolling their Phase 1 / 2 gene therapy trial in patients with FTD- GRN in the second half of 2023~~ . Additional companies, including Kyowa ~~Kiran~~ **Kirin** Co., Ltd. and QurAlis ~~Therapeutics~~ **Corporation** , are conducting preclinical research using ~~gene therapy~~ **genetic medicine** approaches to treat patients with FTD- GRN. Denali Therapeutics Inc. in partnership with Takeda Pharmaceutical Company Limited **,** is conducting a Phase 1 / 2 clinical trial for their recombinant progranulin protein ~~in addition to their oral EIF2a modulator already in a Phase 1 clinical trial~~ . ~~VesperBio~~ --- **Vesper Bio ApS** began ~~Phase 1~~ enrollment ~~for~~ **of a Ph1b / 2a study of** a small molecule sortilin antagonist **in asymptomatic** ~~program targeting FTD-~~ GRN **mutation carriers** in **January** ~~the fourth quarter of 2023~~ **2025** . We are also aware of other therapeutic approaches in preclinical development that may target FTD- GRN patients **, including the Arkuda Therapeutics small molecule progranulin enhancer program. Johnson & Johnson exercised their exclusive option to acquire the Arkuda lysosomal function enhancer portfolio in January 2025. With respect to PBFT02 for the treatment of FTD- C9orf72, our clinical stage competitors are Transposon Therapeutics, Inc., which is conducting a Phase 2 trial with a small molecule autophagy modulator for FTD- C9orf72, and Alector, Inc. (partnered with GSK plc) which conducted a Phase 2 clinical trial for latozinemab in FTD- C9orf72. There are other approaches in preclinical development for the treatment of FTD-C9orf72. In addition to the GRN and C9orf72 targeted therapies, there are two other clinical stage programs targeting the TDP- 43 pathway** . Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical, and other resources than we do, such as larger research and development, clinical, commercial and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. 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 product candidates that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market, if ever. Additionally, new or advanced technologies developed by our competitors may render our current or future product candidates uneconomical or obsolete, and we may not be successful in commercializing our product candidates against competitors. 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 products. Even with the requisite approvals from the FDA in the United States and other ex- U. S. regulatory authorities, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients (which includes caregivers when applicable) and health care payors of 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 ~~59profitable~~ **profitable** . The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including: ● the efficacy, durability 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 ex- U. S. regulatory authorities; ● the willingness of physicians to order genetic testing for potential target patient populations; ● the willingness of potential patients to have genetic testing and counseling; ● the willingness of physicians to prescribe new therapies, including therapies using ICM administration; ● our ability to successfully train neurosurgeons and interventional radiologists in ICM administration of our product candidates; ● the willingness of the target patient population to try new therapies and a therapy with ICM administration; ● the prevalence and severity of any side effects; **58** ● product labeling or product insert requirements of the FDA or ex- U. S. regulatory authorities, including any limitations or warnings contained in a product' s approved labeling; ● relative convenience and ease of administration; ● the strength of marketing and distribution support; ● the timing of market introduction of competitive products and the perceptions of such competitive products compared to our products; ● publicity concerning our products or competing products and treatments; ● the pricing of our products, particularly as compared to alternative treatments; and ● sufficient third- party payor coverage and adequate reimbursement from government and third- party payors and patients' willingness to pay out- of- pocket in the absence of such coverage and adequate reimbursement. Even 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. If in the future we are unable to establish U. S. or global sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if they are approved and we may not be able to generate any revenue. We currently do not have a sales team or marketing team for the sales, marketing, and distribution of any of our product candidates that may receive regulatory approval. In order to commercialize any product candidates after approval, we must build on a territory- by- territory basis sales, reimbursement, distribution, managerial and other non- technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If our product candidates receive regulatory approval, we may decide to establish an internal sales team with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time- consuming and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market. With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory- by- territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval **,** or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses. ~~60We~~ **We** may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay the pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to timely capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. The development of our clinical product candidates and ongoing research programs require significant resources. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. ~~Risks~~ **59Risks** Related to Intellectual Property If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under licensed patents 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 commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other countries for our current product candidates and future products, as well as our core technologies, including our manufacturing know- how. We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business by seeking, maintaining and defending our intellectual property, whether developed internally or licensed from third parties. We also rely on trade secrets, know- how, continuing technological innovation and in- licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy. Additionally, for some of our product candidates, we intend to rely on regulatory protection afforded through rare drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available. Currently, ~~most of~~ our intellectual property protection **includes** ~~consists of~~ patent applications that we have in- licensed from ~~GTP~~ **Penn** under the Penn **License** Agreement. The in- licensed patent applications are directed to certain new AAV capsids, to recombinant AAV viruses, or rAAV, capable of delivering certain genes into human cells to treat disorders of the CNS, to methods of treating those diseases with rAAV, as well as to certain aspects of our manufacturing capabilities and related technologies. Our intellectual property also includes patent applications that we solely own that cover processes that we developed for manufacturing our rAAV products **, methods of treating adult neurodegenerative diseases such as FTD- C9orf72 and ALS and an assay for measuring potency of our rAAV product candidate** . We also have options under the ~~Penn~~ **Gemma Collaboration** Agreement to ~~add~~ **conduct further research into new CNS indications that may create** additional intellectual property ~~to our existing license~~ . 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. The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our own or licensed patent applications will mature into issued patents, and cannot provide any assurances that any such patents, if issued, will include claims with a scope sufficient to protect our current and future product candidates or otherwise provide any competitive advantage. Additionally, patents can be enforced only in those jurisdictions in which the patent has issued. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally twenty years after its first nonprovisional U. S. filing. The natural expiration of a patent outside of the United States varies in accordance with provisions of applicable local law, but is generally 20 years from the earliest local filing date. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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. ~~61Moreover~~ -- **Moreover** , our exclusive license **under the Penn License Agreement** is subject to field restrictions and retained rights, which may adversely impact our competitive position. Our licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates, including biosimilar versions of such products. In addition, the patent portfolio licensed to us is, or may be, licensed to third parties outside our licensed field, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against another licensee or in administrative proceedings brought by or against another licensee in response to such litigation or for other reasons. Other parties have developed technologies that may be related or competitive to our own and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents. Publications of discoveries in the scientific ~~literature~~ **60literature** often lag behind the actual discoveries, and patent applications in the United States and in other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether the inventors of our own or licensed patents and applications were the first to make the inventions claimed in those patents or pending patent applications, or that they were the first to file for patent protection of such inventions. Further, we cannot assure you that all of the potentially relevant prior art relating to our own or licensed patents and patent applications has been found. If such prior art exists, it can invalidate a patent or prevent a patent from issuing from a pending patent application. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Further, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. In addition, the patent prosecution process is expensive and time- consuming, and we or our licensors may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, the scope of the claims initially submitted for examination may be significantly narrowed by the time they issue, if at all. It is also possible that we or our licensors will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We cannot provide any assurances that we will be able to pursue or obtain additional patent protection based on our research and development efforts, or that any such patents or other intellectual property we generate will provide any competitive advantage. Moreover, we do not have the right to control the preparation, filing and prosecution of patent applications, or to control the maintenance of the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be filed, prosecuted or maintained in a manner consistent with the best interests of our business. Even if we acquire patent protection that we expect should enable us to maintain competitive advantage, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability. Third parties, including competitors, may challenge the inventorship, scope, validity, or enforceability thereof, which may result in such patents being narrowed, invalidated or held unenforceable. If issued, our own or licensed patents may be challenged in patent offices in the United States and international markets, or in court. For example, we may be subject to a third- party submission of prior art to the U. S. Patent and Trademark Office, or USPTO, challenging the validity of one or more claims of our own or licensed patents, once

issued. Such submissions may also be made prior to a patent' s issuance, precluding the granting of a patent based on one of our pending ~~own or~~ licensed patent applications. We may become involved in opposition, reexamination, inter partes review, post-grant review, derivation, interference, or similar proceedings in the United States or abroad challenging the claims of patents that we ~~own or~~ have licensed, once issued. Furthermore, patents that we have licensed may be challenged in court, once issued. Competitors may claim that they invented the inventions claimed in such patents or patent applications prior to the inventors of our own or licensed patents, or may have filed patent applications before the inventors of our **own or** licensed patents did. A competitor may also claim that we are infringing its patents and that we therefore cannot practice our technology as claimed under our **own or** licensed patent applications and patents, if issued. As a result, one or more claims of our own or licensed patents may be narrowed or invalidated. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents. Even if they are unchallenged, our own or licensed patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our own or licensed patents by developing similar or alternative technologies or therapeutics in a non- infringing manner. For ~~62example~~ -- **example** , even if we have a valid and enforceable patent, we may not be able to exclude others from practicing our invention if the other party can show that they used the invention in commerce before our filing date or the other party benefits from a compulsory license. Moreover, a third party may develop a competitive product that provides benefits similar to one or more of our product candidates but that uses a vector or an expression construct that falls outside the scope of our patent protection or license rights. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business. Similar risks would apply to any patents or patent applications that we may own or in- license in the future. ~~In~~ **61In** addition to patent protection, if any of our product candidates are approved by the FDA as a biological product under a BLA in the United States, we believe the product would qualify for a 12- year period of exclusivity. Other regulatory exclusivities may be available, such as ~~Orphan~~ **orphan** ~~Drug~~ **drug** exclusivity, with analogous data, marketing, and orphan exclusivities in various foreign countries. However, the scope of such regulatory exclusivities is subject to change, and may not provide us with adequate and continuing protection sufficient to exclude others from commercializing products similar to our product candidates. All of our current product candidates and research programs **, including PBFT02,** are licensed from or based upon licenses from a third- party and are field limited to certain indications. If ~~this~~ **the** license ~~agreement~~ **agreements** ~~is~~ **are** terminated or interpreted to narrow our rights, our ability to advance our current product candidates or develop new product candidates based on these technologies will be materially adversely affected. We currently rely on licenses and sublicenses from third parties, in particular ~~GTP~~ **Penn** , and will continue to rely on third parties for the research, development, manufacturing and commercialization of our current product candidates. If any of our licenses or relationships or any in- licenses on which our licenses are based are terminated or breached, we may: ● lose our rights to develop and market our current product candidates; ● lose patent or trade secret protection for our current product candidates; ● experience significant delays in the development or commercialization of our current product candidates; ● not be able to obtain any other licenses on acceptable terms, if at all; or ● incur liability for damages. Additionally, even if not terminated or breached, our intellectual property licenses or sublicenses may be subject to disagreements over contract interpretation which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations. If we experience any of the foregoing, it could have a materially adverse effect on our business and could force us to cease operations which could cause you to lose all of your investment. If we breach our license agreements it could have a material adverse effect on our commercialization efforts for our product candidates. If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties, we could lose license rights that are important to our business. Our current clinical product candidates ~~and pipeline~~ **, including PBFT02** are ~~, and our anticipated near-term pipeline will be~~ , licensed from ~~GTP~~ **Penn** . Under the Penn **License** Agreement, we are subject to various obligations, including payment obligations, diligence obligations such as development and commercialization obligations, as well as potential royalty payments and other obligations. If we fail to comply with any of these obligations or otherwise breach our license agreements, our licensors may have the right to terminate the applicable license in whole or in part. Generally, the loss of any one of our current licenses, or any other license we may acquire in the future, could harm our business, prospects, financial condition and results of operations. ~~63Licensing~~ -- **Licensing** of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including: ● the scope of rights granted under the license agreement and other interpretation- related issues; ● whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; ● our right to sublicense patent and other intellectual property rights to third parties under collaborative development relationships; ● our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations; **62** ● the ownership of inventions and know- how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and ● whether and the extent to which inventors are able to contest the assignment of their rights to our licensors. If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize the affected product candidates. In addition, if disputes arise as to ownership of licensed intellectual property, our ability to pursue or enforce the licensed patent rights may be jeopardized. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer. Our strategy of obtaining rights to key technologies through in- licenses may not be successful. We seek to expand our product candidate pipeline in part by in- licensing the rights to key technologies. The future growth of our business will depend in part on our ability to in- license or otherwise acquire the rights to additional product

candidates or technologies. We cannot assure you that we will be able to in- license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all. The in- licensing and acquisition of these technologies is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire product candidates or technologies that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to license rights to us. Furthermore, we may be unable to identify suitable product candidates or technologies within our area of focus. If we are unable to successfully obtain rights to suitable product candidates or technologies, our business, financial condition and prospects could suffer. Third parties may initiate legal proceedings alleging claims of intellectual property infringement, the outcome of which would be uncertain and could have a material adverse effect on the success of 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 future products 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 frequent litigation regarding patents and other intellectual property rights. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates, future products and technology. Our competitors or other third parties may assert infringement or misappropriation claims against us, alleging that our therapeutics, manufacturing methods, formulations or administration methods are covered by their patents. Numerous U. S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing product candidates. For example, a third party previously sent us a letter claiming that the use of our AAVhu68 capsid infringes certain patent claims to which the third party has an exclusive license. While this matter has been resolved and we believe that we would have valid defenses to these and any other such claims; however, if any such claims were ultimately successful, we might require a license to continue to use and sell any product candidates using such AAV vector. Such licenses may not be available on commercially reasonable terms, or at all. ~~64Further~~ -- **Further** , we do not know which processes we will use for commercial manufacture of our future products, or which technologies owned or controlled by third parties may prove important or essential to those processes. Given the vast number of patents in our field of technology, we cannot be certain or guarantee that we do not or will not infringe existing patents or that we will not infringe patents that may be granted in the future. Many companies have filed, and continue to file, patent applications related to gene therapy and orphan diseases. Some of these patent applications have already been allowed or issued and others may issue in the future. Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional research and development programs expected in the future. Furthermore, because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of our product candidates or future products. If a ~~patent~~ **63patent** holder believes the manufacture, use, sale, offer for sale or importation of one of our product candidates or future products infringes its patent, the patent holder may sue us even if we have licensed other patent protection for our technology. Moreover, we may face patent infringement claims from non- practicing entities that have no relevant product revenue and against whom our licensed patent portfolio may therefore have no deterrent effect. It is also possible that we have failed to identify relevant third- party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third- party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale, importation or use of a current or future product candidate, or we may incorrectly conclude that a third- party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our future products or the manufacture or use of our future products. Third parties may assert infringement claims against us based on existing intellectual property rights and intellectual property rights that may be granted in the future. If we were to challenge the validity of an issued U. S. patent in court, such as an issued U. S. patent of potential relevance to some of our product candidates or future products or manufacture or methods of use, we would need to overcome a statutory presumption of validity that attaches to every U. S. patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent' s claims. There is no assurance that a court would find in our favor on questions of infringement or validity. Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. If we are found, or believe there is a risk we may be found, to infringe a third- party' s intellectual property rights, we could be required or may choose to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any such 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 access to the same technologies licensed to us. Without such a license, we could be forced, including by court order, to cease commercializing the infringing technology or product. 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. A finding of infringement could prevent us from commercializing our future products or force us to cease some of our business operations, which could materially harm our business. Alternatively, we may need to redesign our infringing products, which may be impossible or require substantial time

and monetary expenditure. If we lose a foreign patent lawsuit alleging our infringement of a competitor' s patents, we could be prevented from marketing our therapeutics in one or more foreign countries and / or be required to pay monetary damages for infringement or royalties in order to continue marketing. Claims that we have misappropriated the confidential information, trade secrets or other intellectual property of third parties could have a similar negative impact on our business. Any of these outcomes would have a materially adverse effect on our business. ~~65Even~~ -- **Even** if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our future products or processes. Patent litigation is costly and time- consuming, and some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. We may not have sufficient resources to bring these actions to a successful conclusion. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts, adversely affect our ability to raise additional funds, and could limit our ability to continue our operations. ~~If~~ **64If** we are unable to protect the confidentiality of our trade secrets, our business and competitive position may be harmed. In addition to the protection afforded by patents, we rely upon unpatented trade secret protection, unpatented know- how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our contractors, collaborators, scientific advisors, employees and consultants and invention assignment agreements with our consultants and employees. We may not be able to prevent the unauthorized disclosure or use of our technical know- how or other trade secrets by the parties to these agreements, however, despite the existence generally of confidentiality agreements and other contractual restrictions. Monitoring unauthorized uses and disclosures is difficult and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the contractors, collaborators, scientific advisors, employees and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. As a result, we could lose our trade secrets. Enforcing a claim that a third- party illegally obtained and is using our trade secrets, like patent litigation, is expensive and time- consuming and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing or unwilling to protect trade secrets. Our trade secrets could otherwise become known or be independently discovered by our competitors. Competitors could purchase our product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected or sufficient to provide an advantage over our competitors, our competitive position could be adversely affected, as could our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets. Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies and our patent protection could be reduced or eliminated for non- compliance with these requirements. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in premature abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non- compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non- payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our product candidates, which would have a material adverse effect on our business. ~~66We~~ **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, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. 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. Further, licensing partners may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States. Competitors may use our technologies in ~~jurisdictions~~ **65jurisdictions** where we have not obtained patent protection to develop their own products and may also export 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. Most of our in- licensed patent families are pending in major pharmaceutical markets including the United States, Canada, Europe, Japan, Korea, and China, as well as other jurisdictions; we will not be able to enforce the patent in any jurisdictions in which the application has

not been filed. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and we or our licensor may be unable to predict and may fail to seek patent protection in jurisdictions in which protection may ultimately be desired. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, 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 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. We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time- consuming and unsuccessful. Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time- consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. The outcome following legal assertions of invalidity and unenforceability is unpredictable. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent' s claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors ~~,~~ and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark ~~67infringement~~ -- **infringement** has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks. Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public 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 material adverse effect on the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail ~~in~~ **66in** such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Changes in patent law in the United States and in ex- U. S. jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our product candidates. As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry ~~involve~~ **involves** both technological and legal complexity, and is therefore costly, time- consuming and inherently uncertain. Past or future patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, in March 2013, under the Leahy- Smith America Invents Act, or America Invents Act, the United States moved from a " first to invent " to a " first- inventor- to- file " patent system. 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 a patent on the invention regardless of whether another inventor had made the invention earlier. The America Invents Act includes a number of other significant changes to U. S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art and establish a new post- grant review system. The effects of these changes are currently unclear as the USPTO continues to promulgate new regulations and procedures in connection with the America Invents Act and many of the substantive changes to patent law, including the " first- inventor- to- file " provisions, only became effective in March 2013. In addition, the courts have yet to address many of these provisions and the applicability of the act and new regulations on the specific patents discussed in this filing have not been determined and would need to be reviewed. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. Additionally, 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. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U. S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, in the case, Assoc. for Molecular Pathology v. Myriad Genetics, Inc., the U. S. Supreme Court held that certain claims to DNA molecules are not eligible for

patent protection. We cannot predict how future decisions by the courts, the U. S. Congress or the USPTO may impact the value of our patents. Any similar adverse changes in the patent laws of other jurisdictions could also have a material adverse effect on our business, financial condition, results of operations and prospects. We may be subject to claims asserting that our employees, consultants, advisors or collaborators have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of or other rights to what we regard as our own or licensed intellectual property. Many of our employees, consultants or advisors, and the employees, consultants or advisors of our licensors, are currently, or were previously, employed at or affiliated with universities, hospitals or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our ~~68employees --~~ **employees**, consultants and advisors do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that 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. Moreover, some of our licensors, and our or our licensors' employees, consultants or advisors are or have been affiliated or have a contractual relationship with multiple institutions and companies including our competitors and may have or have had an obligation to them. Such institutions and companies could challenge our license rights or our licensors' intellectual property ownership rights. Litigation may be necessary to defend against these claims and we may be obligated to indemnify our employees, consultants, advisors or collaborators in certain instances. 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~~ **67In** addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self- executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time. 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. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidates might expire before or shortly after we or our partners commercialize those candidates. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. If we do not obtain patent term extension for any product candidates we may develop, our business may be materially harmed. Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U. S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch- Waxman Amendments. The Hatch- Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per product may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, even if we were to seek a patent term extension, it may not be granted because of, for example, the failure to exercise due diligence during the testing phase or regulatory review process, the failure to apply within applicable deadlines, the failure to apply prior to expiration of relevant patents, or any other failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed. ~~69Some --~~ **Some** of the intellectual property rights that we have in- licensed were generated through the use of U. S. government funding and are therefore subject to federal regulations such as " march- in " rights, certain reporting requirements, and a preference for U. S. based companies. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with ex- U. S. manufacturers. Some of the intellectual property rights we have in- licensed were generated through the use of U. S. government funding and are therefore subject to certain federal regulations. As a result, the U. S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh- Dole Act of 1980, or Bayh- Dole Act, and implementing regulations. These U. S. government rights in certain inventions developed under a government- funded program include a non- exclusive, non- transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U. S. government has the right to require us or our licensors to grant exclusive, partially exclusive, or non- exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as " march- in rights "). The U. S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register ~~the~~ **68the** intellectual property within specified time limits. These time limits have recently been changed by regulation, and may change in the future. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U. S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the

intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U. S. manufacturers may limit our ability to contract with ex- U. S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U. S. government funding, the provisions of the Bayh- Dole Act may similarly apply. Risks Related to Government RegulationThe pricing, 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. Our clinical product candidates currently target indications with small patient populations. In order for products that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such products must be higher, on a relative basis, to account for the lack of volume. Accordingly, we **(including our sublicensees)** will need to implement a coverage and reimbursement strategy for any approved product candidate that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for any future product candidates from third- party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. 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 achieve regulatory approval. Therefore, 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 any of our product candidates will depend substantially, both domestically and internationally, 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 third- party payors. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment. There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U. S. Department of Health and Human Services, since ~~70CMS~~ -- **CMS** decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. However, one payor' s determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Further, a payor' s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours since there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost- containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the EU, the prices of medical products are subject to varying price control mechanisms as part of national health systems. 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 may be required to conduct a clinical trial that compares the cost- effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially ~~lower~~ **69lower** than in the United States. Other countries allow companies to fix their own prices for 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 product candidates may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits. Moreover, increasing efforts by governmental and third- party payors, in the United States and internationally, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. 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 certain third- party payors, such as health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market. In addition to CMS and private payors, professional organizations such as the American Medical Association can influence decisions about reimbursement for new products by determining standards for care. In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our product candidates. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Fast Track Designation by the FDA may not lead to a faster development or regulatory review or approval process. We have obtained Fast Track Designation for PBFT02 for the treatment of FTD- GRN. We may seek Fast Track Designation for **other potential indications for PBFT02, or for** one or more of our other product candidates. 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 needs for this condition, the product sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster

development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. ~~71If~~ **If** we decide to seek Orphan Drug Designation for some of our product candidates, we may be unsuccessful or may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for supplemental market exclusivity. We have obtained Orphan Drug Designation **,** for PBFT02 for the treatment of FTD ~~- GRN~~. We have sought and may continue to seek Orphan Drug Designation for one or more of our other product candidates, and we may be unsuccessful. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as 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 will be recovered from sales in the United States. In the United States, Orphan Drug Designation entitles a party to financial incentives such as tax advantages and user- fee waivers. Opportunities for grant funding toward clinical trial costs may also be available for clinical trials of drugs for rare diseases, regardless of whether the drugs are designated for the orphan use. In addition, if a product that has Orphan Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same product for the same indication for seven years, except in limited circumstances. For large molecule drugs, including gene therapies, sameness is determined based on the principal molecular structural features of a product. As applied to gene therapies, the FDA has recently issued final guidance in which it stated it generally intends to ~~consider~~ **70consider** certain key features, such as the transgenes expressed by the gene therapy and the vectors used to deliver the transgene, to be principal molecular structural features. With regard to vectors, the FDA generally intends to consider whether two vectors from the same viral class are the same or different on a case- by- case basis. The FDA does not intend to consider minor differences between transgenes and vectors to be different principal molecular structural features. When two gene therapy products express the same transgene and have or use the same vector, determining whether two gene therapies are the same drug may also depend on additional features of the final gene therapy product, such as regulatory elements and the cell type that is transduced (for genetically modified cells). In such cases, FDA generally intends to determine whether two gene therapy products are different on a case- by- case basis. Although we have obtained Orphan Drug Designation for our clinical product candidates, and even if we obtain Orphan Drug Designation for additional product candidates in specific indications, we may not be the first to obtain marketing approval of these product candidates for the orphan- designated indication due to the uncertainties associated with developing pharmaceutical products. If a competitor with a product that is determined by the FDA to be the same as one of our product candidates obtains marketing approval before us for the same indication we are pursuing and obtains orphan drug exclusivity, our product candidate may not be approved until the period of exclusivity ends unless we are able to demonstrate that our product candidate is clinically superior. Even after obtaining approval, we may be limited in our ability to market our product. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan- designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different principal molecular structural features can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve the same drug with the same principal molecular structural features for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan Drug Designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek Orphan Drug Designation for some of our product candidates, we may never receive such designations. Similarly, the European Commission may also designate a product as an orphan drug under certain circumstances. ~~72Any~~ **Any** product candidate for which we obtain marketing approval will be subject to extensive post- marketing regulatory requirements and could be subject to post- marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved. Our product candidates and the activities associated with their development and potential commercialization, including their testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, cGMPs, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by the FDA and other regulatory authorities and requirements regarding the distribution of samples to physicians and recordkeeping. The FDA may also impose requirements for costly post- marketing studies or clinical trials and surveillance to monitor the safety or efficacy of any approved product. The FDA closely regulates the post- approval marketing and promotion of drugs and biologics to ensure drugs and biologics are marketed only for the approved indications and in accordance with the provisions of the approved product labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use of their products. If we promote our product candidates beyond their potentially approved indications, we may be subject to enforcement action for off- label promotion. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws. ~~In~~ **71In** addition, later discovery of previously unknown adverse events or other problems with our product candidates, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including: ● restrictions on such product candidates,

manufacturers or manufacturing processes; ● restrictions on the labeling or marketing of a product; ● restrictions on product distribution or use; ● requirements to conduct post- marketing studies or clinical trials; ● warning or untitled letters; ● withdrawal of any approved product from the market; ● refusal to approve pending applications or supplements to approved applications that we submit; ● recall of product candidates; ● fines, restitution or disgorgement of profits or revenues; ● suspension or withdrawal of marketing approvals; ● refusal to permit the import or export of our product candidates; ● product seizure; or ● injunctions or the imposition of civil or criminal penalties. Non- compliance with European requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with requirements regarding the protection of personal information can also lead to significant penalties and sanctions. Our product candidates for which we intend to seek approval may face competition from biosimilars approved through an abbreviated regulatory ~~pathwayThe~~ --- **pathway. The** Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the ACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA. The BPCIA created an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference ~~73product~~ -- **product** . Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product is approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. We believe that if any of our product candidates is approved as a biological product under a BLA, it should qualify for the 12- year period of exclusivity. However, there is a risk that the FDA will not consider any of our product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Moreover, an interchangeable biosimilar, once approved, may be substituted under existing law for any one of our reference products in a way that is similar to traditional generic substitution; any non- interchangeable biosimilar products may also be substituted by a health care provider but, under existing law, will not be automatically substituted at the pharmacy. The extent of the impact of such substitution will depend on a number of marketplace and regulatory factors that are still developing. Finally, there has been public discussion of potentially decreasing the period of exclusivity from the current 12 years. If such a change were to be enacted, our product candidates, if approved, could have a shorter period of exclusivity than anticipated. ~~Enacted~~ **72Enacted** and future legislation may affect pricing and third- party payment for our product candidates, may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set. The full effect of recent United States healthcare reform and other changes in the healthcare industry, laws, and regulations and in healthcare spending is currently unknown, and the reform and other changes may adversely affect our business model. In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, affect pricing and third- party payment for our product candidates prevent or delay marketing approval of our product candidates, restrict or regulate post- approval activities and negatively affect our ability to profitably sell any products for which we obtain marketing approval. The commercial potential for our products, if any, could be affected by changes in healthcare spending and policy in the United States and abroad. New laws, regulations, or judicial decisions or new interpretations of existing laws, regulations, or decisions, related to healthcare availability, the method of delivery, or payment for healthcare products and services could adversely affect our business, operations, and financial condition, if and when we are able to obtain marketing approval and commercialize our products. There have been and continue to be a number of initiatives at the U. S. federal and state levels that seek to reduce healthcare costs in general and the cost of pharmaceuticals in particular. For example, the Budget Control Act imposed, subject to certain temporary suspension periods, 2 % reductions in Medicare payments to providers per fiscal year starting April 1, 2013 **,** and, due to subsequent legislative amendments to the statute, will remain in effect through 2031, unless additional Congressional action is taken. In December 2020, CMS issued a final rule implementing significant manufacturer price reporting changes under the Medicaid Drug Rebate Program, including an alternative rebate calculation for a line extension that is tied to the price increases of the original drug, and Best Price reporting related to certain value- based purchasing arrangements. Under the American Rescue Plan Act of 2021, effective January 1, 2024, the statutory cap on Medicaid Drug Rebate Program rebates that manufacturers pay to state Medicaid programs is eliminated. Elimination of this cap may, in some cases, require pharmaceutical manufacturers to pay more in rebates than they receive on the sale of products. It is unclear to what extent these regulations or any future legislation or regulations will affect our business, including our ability to generate revenue and achieve profitability. There has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several presidential executive orders, Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare, and reform government program reimbursement methodologies for drug products. The FDA released a final rule in September 2020 ~~74providing~~ -- **providing** guidance for states to build and submit importation plans for drugs from Canada, and **the** FDA authorized the first such plan in Florida in January 2024. Recently, several healthcare reform initiatives culminated in the enactment of the **Inflation Reduction Act, or** IRA **,** in August 2022, which allows, among other things, **the U. S. Department of Health and Human Services, or** HHS **,** to negotiate the selling price of a statutorily specified number of drugs and biologics each year that CMS reimburses under Medicare Part B and Part D. Only high- expenditure single- source biologics that have been approved for at least 11 years (~~7~~ **seven** years for single- source drugs) can qualify for negotiation, with the negotiated price taking effect two years after the selection year. Negotiations for Medicare Part D products ~~begin~~ **began** in 2024 with the

negotiated price taking effect in 2026, and negotiations for Medicare Part B products begin in 2026 with the negotiated price taking effect in 2028. In August 2023, HHS announced the ten Medicare Part D drugs and biologics that it selected for negotiations, and by October 1, 2023, each manufacturer of the selected drugs signed a manufacturer agreement to participate in the negotiations. HHS ~~will announce~~ **announced** the negotiated maximum fair prices ~~by September 1~~ **on August 15** , 2024, and ~~this~~ **these** price ~~cap~~ **caps** , which cannot exceed ~~a~~ **the** statutory ceiling price, will come into effect on January 1, 2026. A drug or biological product that has an orphan drug designation for only one rare disease or condition will be excluded from the IRA' s price negotiation requirements, but loses that exclusion if it has designations for more than one rare disease or condition, or if is approved for an indication that is not within that single designated rare disease or condition, unless such additional designation or such disqualifying approvals are withdrawn by the time CMS evaluates the drug for selection for negotiation. The IRA ~~also~~ **73also** imposes rebates on Medicare Part B and Part D drugs whose prices have increased at a rate greater than the rate of inflation. In addition, the law eliminates the " donut hole " under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out- of- pocket cost and establishing a new manufacturer discount program, which requires manufacturers that want their drugs to be covered by Medicare Part D to provide statutorily defined discounts to Part D enrollees. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through ~~plan~~ **the** year 2025. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, some significant, including civil monetary penalties. These provisions ~~are~~ **began** taking effect progressively starting in 2023, although they may be subject to legal challenges. For example, the provisions related to the negotiation of selling prices of high-expenditure single- source drugs and biologics have been challenged in multiple lawsuits. Thus, it is unclear how the IRA will be implemented but it will likely have a significant impact on the pharmaceutical industry and the pricing of our products and product candidates. The adoption of restrictive price controls in new jurisdictions, more restrictive controls in existing jurisdictions or the failure to obtain or maintain timely or adequate pricing could also adversely impact revenue. We expect pricing pressures will continue globally. Further, at the U. S. state level, legislatures are increasingly enacting laws and implementing regulations designed to control pharmaceutical and biological product pricing, including price or reimbursement constraints, discount requirements, marketing cost disclosure and price increase transparency reporting, and programs designed to encourage importation from other countries and bulk purchasing. Additional state and federal healthcare reform measures may be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services or otherwise negatively impact our business model. Our operations and relationships with customers and third- party payors will be subject to applicable anti- kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to penalties including criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Healthcare providers and third- party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any product candidates for which we obtain marketing approval. Restrictions under applicable U. S. federal and state healthcare laws and regulations may include the following: ● the federal Anti- Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, ~~75to~~ **to** induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid; ● federal false claims laws, including the federal False Claims Act, imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; ● the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for, among other things, knowingly and willfully executing or attempting to execute 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, or HITECH, Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain types of people and entities with respect to safeguarding the privacy, security and transmission of individually identifiable health information; ● the federal Physician Payment Sunshine Act requires applicable manufacturers of covered drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children' s Health Insurance Program, with specific exceptions, to report payments and other transfers of ~~value~~ **74value** to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, certain types of advanced practice nurses, and teaching hospitals, as well as certain ownership and investment interests held by physicians and their immediate family, which includes annual data collection and reporting obligations; and ● analogous state and foreign laws and regulations, such as state anti- kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by 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 drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Other state laws require reporting of certain pricing information, including price increases and prices of newly launched drugs. 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. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. 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 product candidates from government- funded healthcare programs, such as Medicare and Medicaid, disgorgement, oversight monitoring, contractual damages, reputational harm, diminished profits and future earnings, 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. Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our BusinessOur future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel. We are highly dependent on the research and development, clinical and business development expertise of our management, scientific and clinical team. We also benefit from the research expertise of Dr. Wilson ~~, our Chief~~ **. In his capacity as a** Scientific Advisor **, Dr. Wilson is not involved in day- to- day operations and does not have the ability to control or significantly influence the management or operating policies of the Company** . Although we have entered into a consulting agreement with Dr. Wilson, he may terminate his relationship with ~~76us~~ **us** at any time. Although we have entered into employment letter agreements or employment agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain " key person " insurance for any of our executives or other employees. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and manufacturing strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited. Recruiting and retaining qualified scientific, clinical, manufacturing and, if needed, sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize drugs, particularly within the gene therapy space. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous ~~pharmaceutical~~ **75pharmaceutical** and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel. Further, the reductions in **our** workforce announced in ~~March~~ 2022, ~~November 2022, and July~~ 2023 **, and January 2025** may also make retention of our current personnel both more important and more challenging. These workforce reductions resulted in the loss of longer- term employees, the loss of institutional knowledge and expertise and the reallocation and combination of certain roles and responsibilities across the organization, all of which could adversely affect our operations. Given the complexity of our business, we must continue to implement and improve our managerial, operational and financial systems, manage our facilities and continue to recruit and retain qualified personnel. ~~Given the complexity of our business, we must continue to implement and improve our managerial, operational and financial systems, manage our facilities and continue to recruit and retain qualified personnel.~~ We may be required to expand our manufacturing, development and regulatory capabilities in the future, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. We may be required to expand our manufacturing, development and regulatory capabilities in the future, which could result in growth to the number of our employees and the scope of our operations, particularly in the areas of manufacturing and clinical strategy, and growing our capability to conduct clinical trials. We may not be able to effectively manage the expansion of our operations in the future or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations. Our internal computer systems, or those of our third- party collaborators or other contractors, may fail or suffer security breaches and cyber **-** attacks, which could result in a material disruption of our development programs. We believe that we take reasonable steps that are designed to protect the security, integrity and confidentiality of the information we collect, use, store, and disclose, but inadvertent or unauthorized data access may occur despite our efforts. For example, our system protections may be ineffective or inadequate, or we could be impacted by software bugs or other technical malfunctions, as well as employee error or malfeasance. Additionally, privacy and data protection laws are evolving, and it is possible that these laws may be interpreted and applied in a manner that is inconsistent with our data handling safeguards and practices that could result in fines, lawsuits, and other penalties, and significant changes to our or our third- party partners business practices and products and service offerings. To the extent that the measures we or our third- party business partners have taken prove to be insufficient or inadequate, we may become subject to litigation, breach notification obligations, or regulatory or administrative sanctions, which could result in significant fines, penalties, damages, harm to our reputation or loss of patients. While we have not experienced any material losses as a result of any system failure, accident or security breach to date, we have been the subject of certain phishing attempts in the past. If such an event were to occur and cause interruptions in our operations, it could result in a material ~~77disruption~~ -- **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. Additionally, a party who circumvents our security measures could, among other effects, appropriate patient information or other proprietary data, cause interruptions in our operations, or expose patients to hacks, viruses, and other disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase

our costs to recover or reproduce the data. In addition, insurance coverage to compensate for any losses associated with such events may not be adequate to cover all potential losses. 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 increasingly sophisticated. To the extent that any disruption, security breach, or cyber- attack were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Depending on the nature of the information compromised, in the event of a data breach or other unauthorized access to our patient data, we may also have obligations to notify patients and regulators about the incident, and we may need to provide some form of remedy, such as a subscription to credit monitoring services, pay significant fines to one or more regulators, or pay compensation in connection with a class- action settlement (including under the new private right of action under the California Consumer Privacy Act of 2018, or the CCPA, which is expected to ~~increase~~ **76increase** security breach litigation). Such breach notification laws continue to evolve and may be inconsistent from one jurisdiction to another. Complying with these obligations could cause us to incur substantial costs and could increase negative publicity surrounding any incident that compromises patient data. Additionally, the financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we may maintain, and there can be no assurance that the limitations of liability in any of our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above. Any of the foregoing could have an adverse effect on our business, reputation, operating results, and financial condition. Our ability to utilize our net operating loss carryforwards may be subject to limitation. As of December 31, ~~2023~~ **2024** , we had federal **and state** net operating loss, or NOL, carryforwards of $ ~~265~~ **339** . ~~5~~ **1 million, and local NOL carryforwards of $ 218. 8** million. $ 0. 3 million of the federal NOLs will begin to expire in 2037, ~~if not used prior to that date,~~ and the remainder will carryforward indefinitely. **Our** ~~As of December 31, 2023, we had~~ state NOL carryforwards ~~of $ 265. 5 million, which~~ will begin to expire in 2037, and expire through ~~2043~~ **2044** . ~~As of December 31~~ , **and our** ~~2023, we had~~ local NOL ~~carryforwards of $ 214. 5 million, which will begin~~ **began** to expire in 2024 ~~,~~ and expire through ~~2043~~ **2044** . To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any. ~~Under legislative changes made by U. S. federal tax legislation, commonly referred to as the Tax Cuts and Jobs Act, or the TCJA,~~ U. S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the ability to utilize such federal net operating losses to offset taxable income is limited to 80 % of our taxable income ~~before the~~ **(without regard to certain** ~~deduction~~ **deductions)** ~~for such net operating loss carryovers. It is uncertain if and to what extent various states will conform to the TCJA~~ . Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the ~~IRC~~ **Code** , if a corporation undergoes an " ownership change, " generally defined as a greater than 50 % change (by value) in its equity ownership over a three- year period, the corporation' s ability to use its pre- change NOLs and other pre- change tax attributes (such as research tax credits) to offset its post- change income and post- change **tax** liability may be limited. We have not undertaken a Section 382 study, and it is possible that we have previously undergone one or more ownership changes so that our use of net operating losses is **currently limited** ~~subject to limitation~~ . We may experience ownership changes in the future as a result of ~~subsequent~~ **equity offerings or other** shifts in our stock ownership **, some of which are outside of our control** . As a result, **even** if we earn net taxable income, our ability to use our pre- change NOLs **and other tax attributes** to offset ~~U. S. federal~~ taxable income **and tax liability** may be subject to limitations, which could potentially result in increased future tax liability ~~78to~~ **to** us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed **. Any such limitations may result in greater tax liabilities than we would incur in the absence of such limitations and any increased liabilities could adversely affect our business, results of operations, financial position and cash flows** . U. S. federal income tax reform and changes in other tax laws could adversely affect us. Tax laws are being re- examined and evaluated globally, and tax authorities are increasingly scrutinizing the tax positions of companies. Changes in tax laws and regulations in federal, state, local, and foreign jurisdictions could have material adverse impacts on our business, cash flows, operating results, or financial condition, and could materially affect our tax obligations and effective tax rate. For example, the Tax Cuts and Jobs Act significantly reformed the ~~Internal Revenue Code of 1986, as amended, or the~~ Code. This legislation, among other things, included changes to U. S. federal tax rates, imposed significant additional limitations on the deductibility of interest and the use of net operating losses generated in tax years beginning after December 31, 2017. Beginning in 2022, the Tax Cuts and Jobs Act also eliminated the option to immediately deduct research and development expenditures and required taxpayers to amortize domestic expenditures over five years and foreign expenditures over fifteen years. Changes in corporate tax rates, the realization of net deferred tax assets, and the deductibility of expenses under the Tax Cuts and Jobs Act or future changes in tax laws could have a material impact on the value of our deferred tax assets, could result in significant one- time charges in the current or future taxable years, and could increase our future U. S. tax expense. In addition, it is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act or any newly enacted federal tax legislation. Changes in tax laws or regulations in the various tax jurisdictions we are subject to that are applied adversely to us or our clients could increase the costs of our products and harm our business. Additionally, we use our best judgment in attempting to quantify and reserve for our tax obligations. However, a challenge by a taxing authority, a limitation on our ability to utilize tax benefits such as carryforwards or tax credits, or a ~~deviation~~ **77deviation** from other tax- related assumptions could have a material adverse effect on our business, results of operations, or financial condition. Our employees, principal investigators, CROs and consultants 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 and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of FDA and ex- U. S. regulators, provide accurate information to the FDA and ex- U. S. regulators, 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, pricing, discounting, 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 may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, 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 governmental 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, including the imposition of significant fines or other sanctions. 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 will face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and will face an even greater risk if we commercialize any of our product candidates. If we cannot successfully defend ~~79ourselves~~ **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; ● injury to our reputation and significant negative media attention; ● initiation of investigations by regulators; ● withdrawal of clinical trial participants; ● significant time and expenses to defend the related litigation; ● diversion of management and scientific resources from our business operations; ● substantial monetary awards to trial participants or patients; ● loss of revenue; and ● the inability to commercialize any product candidates that we may develop. We currently hold limited product liability insurance coverage. We will need to purchase additional product liability insurance coverage as we expand our clinical trials, and if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. A successful product liability claim or series of claims brought against us, could decrease our cash and adversely affect our business and financial condition. ~~We~~ **78We** are subject to U. S. and certain foreign export and import controls, sanctions, embargoes, anti- corruption laws, and anti- money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations that can harm our business. We are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Controls, the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, and other state and national anti- bribery and anti- money laundering laws in the countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other partners from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase, and / or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government- affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other partners, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. Risks Related to Our Common StockThe price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for holders of our common stock. Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including: ● results of preclinical studies or clinical trials of our product candidates or those of our competitors; ● unanticipated or serious safety concerns related to the use of any of our product candidates; ~~80~~ ● adverse regulatory decisions, including failure to receive regulatory approval for any of our product candidates; ● the success of competitive drugs or technologies; ● regulatory or legal developments in the United States and other countries applicable to our product candidates; ● the size and growth of our prospective patient populations; ● developments concerning our collaborators, our external manufacturers or in- house manufacturing capabilities; ● inability to obtain adequate product supply for any product candidate for preclinical studies, clinical trials or future commercial sale or inability to do so at acceptable prices; ● 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 drugs; ● actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts or publications of research reports about us or our industry; ● variations in our financial results or those of companies that are perceived to be similar to us; ● changes in the structure of healthcare payment systems; ● market conditions in the biotechnology sector; **79** ● our cash position or the announcement or expectation of additional financing efforts; ● health pandemics could adversely impact our business, including our clinical trials and clinical trial operations; ● general economic, industry and market conditions, including ~~rising~~ **changes in** interest rates **, tariffs** , market volatility, a potential federal government shutdown and inflation; ● general

economic uncertainty and capital markets disruptions, which has been substantially impacted by geopolitical instability due to the ongoing military conflicts around the world; and ● other factors, including those described in this " Risk Factors " section, many of which are beyond our control. Our executive officers, directors, principal stockholders and their affiliates exercise significant influence over our company, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control. As of December 31, ~~2023~~ **2024** , our executive officers, directors, beneficial owners of 5 % or more of our capital stock and their respective affiliates beneficially owned shares representing a substantial portion of our capital stock. This group of stockholders may have the ability to control us through this ownership position and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock **. The price of our common stock does not meet the requirements for continued listing on The Nasdaq Global Select Market or The Nasdaq Capital Market. If we fail to regain compliance with the minimum listing requirements, our common stock will be subject to delisting. Our ability to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if our common stock is delisted. The continued listing standards of The Nasdaq Global Select Market, require, among other things, that the minimum bid price of a listed company' s stock be at or above $ 1. 00. On August 1, 2024, the Company received notice from the Listing Qualifications staff of The Nasdaq Stock Market, LLC, that, because the closing bid price for the Company' s common stock had fallen below $ 1. 00 per share for 30 consecutive business days, the Company no longer complies with the minimum bid price requirement for continued listing on The Nasdaq Global Select Market. Pursuant to Nasdaq Listing Rule 5810 (c) (3) (A), the Company was provided an initial compliance period of 180 calendar days, or until January 28, 2025, to regain compliance with the minimum bid price requirement. The Company did not regain compliance by January 28, 2025. In January 2025, the Company applied to Nasdaq for an additional 180 calendar day compliance period and, in connection with such application, applied to transfer the listing of our common stock from The Nasdaq Global Select Market to The Nasdaq Capital Market. Nasdaq approved our transfer application effective on January 29, 2025, and the listing of our common stock transferred to The Nasdaq Capital Market effective as of the opening of business on January 30, 2025. To regain compliance, the closing bid price of the Company' s common stock must meet or exceed $ 1. 00 per share for a minimum of 10 consecutive business days prior to July 28, 2025. To attempt to regain compliance with Nasdaq' s requirements, we intend to seek stockholder approval for a reverse stock split. We cannot provide any assurances that we will obtain stockholder approval for a reverse stock split, or that any reverse stock split would result in any sustained increase in the market price of our common stock. Because a reverse stock split will reduce the number of shares of common stock available in the public market, the trading market for common stock may be harmed, particularly if the stock price does not increase as a result of a reverse stock split. We cannot provide any guarantee that we will regain compliance during the grace period or be able to maintain compliance with Nasdaq' s listing requirements in the future. If we are not able to regain compliance during the additional 80compliance period, or any other extension of the compliance period for which we may be eligible, our common stock will be subject to delisting. If Nasdaq delists our securities for trading on The Nasdaq Capital Market, we could face significant adverse consequences. Delisting from The Nasdaq Capital Market would likely have an adverse effect on the price of our common stock and could impair your ability to sell or purchase our common stock when you wish to do so. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities** . Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain. We have never declared or paid any cash dividends on our common stock and do not currently intend to do so for the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will be limited to the appreciation of stock. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in value of the stock. We cannot guarantee you that shares ~~81of~~ **of** our common stock will appreciate in value or even maintain the price at which our stockholders have purchased their shares. If we fail to establish and maintain proper and effective internal control over financial reporting in the future, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, investors' views of us and, as a result, the value of our common stock. Pursuant to Section 404 of the Sarbanes- Oxley Act of 2002, or Sarbanes- Oxley Act, we are required to furnish a report by our management on our internal control over financial reporting within our Form 10- K. However, while we remain either a small reporting or emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time- consuming effort that will need to be frequently evaluated. Our failure to maintain the effectiveness of our internal controls in accordance with the requirements of the Sarbanes- Oxley Act could have a material adverse effect on our business. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. In addition, if we are not able to continue to meet these requirements, we may not be able to remain listed on Nasdaq. We expect to hire additional personnel and may utilize external temporary resources to implement, document and modify policies and procedures to maintain effective internal controls.

However, it is possible that we may identify deficiencies and weaknesses in our internal controls. If material weaknesses or deficiencies in our internal controls exist and go undetected or unremediated, our financial statements could contain material misstatements that, when discovered in the future, could cause us to fail to meet our future reporting obligations and cause the price of our common stock to decline. We will continue to incur increased costs as a result of operating as a public company and our management will continue to be required to devote substantial time to new compliance initiatives. As a public company, particularly after we are no longer an " emerging growth company, " we will continue to incur significant legal, accounting and other expenses. In addition, the Sarbanes- Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time- consuming and costly. We are an " emerging growth company " and " smaller reporting company, " and the reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies may make our common stock less attractive to investors. ~~We~~ **81We** are an " emerging growth company, " as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of (i) the last day of the fiscal year in which we have total annual gross revenue of $ 1. 235 billion or more; (ii) December 31, 2025; (iii) the date on which we have issued more than $ 1. 0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the market value of our common stock that is held by non- affiliates exceeds $ 700. 0 million as of the last business day of our most recently completed second fiscal quarter. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include: ● not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes- Oxley Act; ● not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor' s report providing additional information about the audit and the financial statements; ~~82~~ ● being permitted to present only two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced " Management' s Discussion and Analysis of Financial Condition and Results of Operations " disclosure in this Form 10- K; ● reduced disclosure obligations regarding executive compensation; and ● exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We may choose to take advantage of some, but not all, of the available exemptions. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes- Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period ~~for~~ **to** ~~complying~~ --- **comply** with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same adoption timelines for new or revised accounting standards as other public companies that are not emerging growth companies. We are also a " smaller reporting company, " meaning that the market value of our stock held by non- affiliates is less than $ 700. 0 million and our annual revenue is less than $ 100. 0 million during the most recently completed fiscal year. We will continue to be a smaller reporting company if either (i) the market value of our stock held by non- affiliates is less than $ 250. 0 million or (ii) our annual revenue is less than $ 100. 0 million during the most recently completed fiscal year and the market value of our stock held by non- affiliates is less than $ 700. 0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10- K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation. ~~The~~ **82The** exclusive forum provisions in our restated certificate of incorporation and amended and restated bylaws may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims. Our restated certificate of incorporation, to the fullest extent permitted by law, provides that the Court of Chancery of the State of Delaware will be the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, or the DGCL, our restated certificate of incorporation, or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision does not apply to suits brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended, or the Exchange Act. It could apply, however, to a suit that falls within one or more of the categories enumerated in the exclusive forum provision and asserts claims under the Securities Act, inasmuch as Section 22 of the Securities Act, creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rule and regulations thereunder. There is uncertainty as to whether a court would enforce such provision with respect to claims under the Securities Act, and our stockholders will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder. **Our** ~~In March 2020, we~~ amended and

~~restated our~~ restated bylaws ~~to~~ **also** provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or a Federal Forum Provision. Our decision to adopt a ~~83Federal --~~ **Federal** Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court. These choice of forum provisions may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provisions contained in our restated certificate of incorporation or amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations and financial condition. In addition, Section 203 of the DGCL may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15 % or more of our common stock. Provisions in our corporate charter documents and under 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 restated certificate of incorporation and our restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also 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 so that not all members of our board are elected at one time; ● permit only the board of directors to establish the number of directors and fill vacancies on the board; ● provide that directors may only be removed " for cause " and only with the approval of two- thirds of our stockholders; **83** ● require super- majority voting to amend some provisions in our restated certificate of incorporation and restated bylaws; ● authorize the issuance of " blank check " preferred stock that our board could use to implement a stockholder rights plan, also known as a " poison pill "; ● eliminate the ability of our stockholders to call special meetings of stockholders; ● prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders; ● prohibit cumulative voting; and ● establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings. Moreover, we are governed by the provisions of Section 203 of the DGCL, 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. Any of these provisions of our charter documents or Delaware law could, under certain circumstances, depress the market price of our common stock. ~~84General --~~ **General** Risk FactorsWe may be subject to securities litigation, which could result in substantial expenses and could divert management attention. The market price of our common stock has been and may continue to be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management' s attention from other business concerns, which could seriously harm our business. If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline. The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. We do not have any control over the analysts **,** or the content and opinions included in their reports. If one or more of the analysts covering our business ~~downgrade~~ **downgrades** their evaluations of our stock, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline. We are subject to a variety of privacy and data security laws, and our failure to comply with them could harm our business. We maintain a large quantity of sensitive information, including confidential business and personal information in connection with the operation of our business, and are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. Each of these constantly evolving laws can be subject to varying interpretations. Additionally, the SEC and many jurisdictions have enacted or may enact laws and regulations requiring companies to disclose or otherwise provide notifications regarding ~~data~~ **84data** security breaches. For example, the SEC recently adopted cybersecurity risk management and disclosure rules, which require the disclosure of information pertaining to cybersecurity incidents and cybersecurity risk management, strategy, and governance. In addition, states are constantly adopting new laws or amending existing laws, requiring attention to frequently changing regulatory requirements with inconsistent or conflicting standards. For example, California has enacted the CCPA, which became operative on January 1, 2020 and became enforceable by the California Attorney General on July 1,

2020. Additionally, in the California Privacy Rights Act, or CPRA, which expands upon the CCPA, became effective on January 1, 2023. The CCPA and CPRA require covered companies to, among other things, provide new disclosures to California users, and affords such users new privacy rights such as the ability to opt- out of certain sales of personal information and expanded rights to access and require deletion of their personal information, opt- out of certain personal information sharing, and receive detailed information about how their personal information is collected, used, and shared. The CCPA and CPRA provide for civil penalties for violations, as well as a private right of action for security breaches that may increase security breach litigation. Potential uncertainty surrounding the CCPA and CPRA may increase our compliance costs and potential liability, particularly in the event of a data breach, and could have a material adverse effect on our business, including how we use personal information, our financial condition, the results of our operations or prospects. Virginia' s Consumer Data Protection Act, which took effect on January 1, 2023, requires opt- in consent from consumers to acquire and process their sensitive personal information, which includes information revealing a consumer' s physical and mental health diagnosis and genetic and biometric information that can identify a consumer. ~~85Other --~~ **Other** states ~~including Colorado, Connecticut and Utah~~ have passed similar laws, and a number of other states are actively considering bills with similar laws. To the extent multiple state- level laws are later introduced, it may require costly and difficult efforts to achieve compliance with such laws that could expose us to fines and penalties for non- compliance. In the European Economic Area, or the EEA, the General Data Protection Regulation or the GDPR, governs the collection, use, disclosure, transfer or other processing of personal data of European persons. Among other things, the GDPR imposes requirements regarding the security of personal data and notification of data processing obligations to the competent national data processing authorities, changes the lawful bases on which personal data can be processed, expands the definition of personal data and requires changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States and other jurisdictions that the European Commission does not recognize as having " adequate " data protection laws (sometimes referred to as " third countries "), and imposes strict rules subject to substantial fines for breaches and violations (up to the greater of € 20 million or 4 % of our annual worldwide gross revenue). These obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other requirements or our practices. Additionally, in the United Kingdom, or U. K., the Data Protection Act contains provisions, including its own derogations, for how GDPR is applied in the U. K. We have to continue to comply with the GDPR and also the U. K.' s Data Protection Act, with each regime having the ability to fine up to the greater of € 20 million (£ 17 million) or 4 % of global turnover. As of January 1, 2024, although effective July 10, 2023, the new EU- U. S. Data Privacy Framework, or DPF, has been recognized as adequate under EU law to allow transfers of personal data from the EU (as well as the U. K. and Switzerland) to certified companies in the U. S. However, the DPF is likely to face legal challenge at the Court of Justice of the European Union which could cause the legal requirements for personal data transfers from the Europe to the U. S. to become uncertain once again. We will monitor these legal developments and continue to use best practices to follow established European legal standards to conduct cross- border transfer of personal data. In addition, while the ~~CJEU~~ **Court of Justice of the European Union** upheld the adequacy of the standard contractual clauses (a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism, and potential alternative to the Privacy Shield), it made clear that reliance on them alone may not necessarily be sufficient in all circumstances. Use of the standard contractual clauses must now be assessed on a case **-** by **-** case basis, taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals. The use of standard contractual clauses for the transfer of personal data specifically to the United States ~~remains~~ **85remains** under review by a number of European data protection supervisory authorities, along with those of some other EU member states. German and Irish supervisory authorities have indicated, and enforced in recent rulings, that the standard contractual clauses alone provide inadequate protection for EU- U. S. data transfers. Further, on June 4, 2021 the European Commission finalized new versions of the Standard Contractual Clauses, with the Implementing Decision now in effect as of June 27, 2021. To comply with the Implementing Decision and the new Standard Contractual Clauses, we may need to implement additional safeguards to further enhance the security of data transferred out of the EEA, conduct data transfer impact assessments, and review existing agreements which could increase our compliance costs, expose us to further regulatory scrutiny and liability, and adversely affect our business. The new standard contractual clauses apply only to the transfer of data outside of the EEA and / or Switzerland and not the United Kingdom, though the U. K.' s Information Commissioner' s Officer launched a public consultation on its draft international data transfer agreement in August 2021, and subsequently issued a new international data transfer agreement and addendum which we are required to use under Article 46 of the U. K. GDPR when making restricted data transfers outside of the U. K. 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 these and any other applicable privacy and data security laws and regulations is a rigorous and time- intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data ~~86protection --~~ **protection** rules. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations. Furthermore, the laws are not consistent, and compliance in the event of a widespread data breach is costly. We generally seek to comply with industry standards and are subject to the terms of our privacy policies and privacy- related obligations to third parties. We strive to comply with all applicable laws, policies, legal obligations and industry codes of conduct relating to privacy and data protection to the extent possible. However, it is possible that these obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other rules or our practices. Any failure or perceived failure by us, even if unfounded, to comply with applicable privacy and data security laws and regulations, our privacy policies, or our privacy- related obligations to users or other third parties, or any compromise of security that results in the unauthorized release

or transfer of personal information or other sensitive data, may result in governmental enforcement actions, litigation, or public statements against us by consumer advocacy groups or others and could cause our users to lose trust in us, which would have an adverse effect on our reputation and business. Any significant change to applicable laws, regulations or industry practices regarding the use or disclosure of our users' data, or regarding the manner in which the express or implied consent of users for the use and disclosure of such data is obtained – or in how these applicable laws, regulations or industry practices are interpreted and enforced by state, federal and international privacy regulators – could require us to modify our practices, possibly in a material manner, may subject us to regulatory enforcement actions and fines, and may limit our ability to operate using the data that was voluntarily shared with us. Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations. Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the global financial crisis caused extreme volatility and disruptions in the capital and credit markets, and, in recent months, the global economy has been impacted by ~~increasing~~ **fluctuating** interest rates **, tariffs,** and inflation. Likewise, the capital and credit markets may be adversely affected by the ongoing conflicts in Ukraine and the Middle East, the possibility of a wider European or global conflict, global sanctions imposed in response thereto, and potential recessions. Moreover, there has been recent turmoil in the global banking system. **We** ~~For example, in March 2023, Silicon Valley Bank, SVB, was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation, or FDIC, as receiver. While we did not hold any cash directly at SVB or other banking institutions that have since failed, we~~ regularly maintain cash balances at third- party financial institutions in excess of the FDIC insurance limit and there is no guarantee that the federal government would guarantee all depositors if such financial institutions were to fail, as they did with SVB depositors, in the event of further bank closures and continued instability in the global banking system. A severe or prolonged economic downturn, such as the global financial crisis, could result in a variety of risks to our business, ~~including~~ **86including** , weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business. We or the third parties upon whom we depend may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster. Natural disasters could severely disrupt our operations and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our manufacturing facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. In addition, the long- term effects of climate change on general economic conditions and the pharmaceutical industry in particular are unclear, and may heighten or intensify existing risk of natural disasters. The disaster recovery and business continuity plans we have in place may prove inadequate in ~~87the~~ -- **the** event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. ~~88Item~~ **87Item** 1B. Unresolved Staff ~~CommentsNone~~ **CommentsNone88** ~~89~~