Risk Factors Comparison 2024-02-29 to 2023-02-21 Form: 10-K

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The following risk factors and other information included in this Annual Report on Form 10- K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10- K for a discussion of some of the forward- looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. Risks Related to the Development and Commercialization of our Products and our Product ~~Candidates~~**If Candidates****We may be unable to continue to commercialize Translarna for nmDMD in the EEA if the EC adopts the negative opinion issued by the CHMP for the renewal of the existing conditional authorization for Translarna. Our marketing authorization for Translarna for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged two years and older in the EEA is subject to annual review and renewal by the EC following reassessment by the EMA of the benefit- risk balance of the authorization. In September 2022, we submitted a Type II variation to the EMA to support conversion of the conditional marketing authorization for Translarna to a standard marketing authorization, which included a report on the placebo- controlled trial of Study 041 and data from the open- label extension. In February 2023, we also submitted an annual marketing authorization renewal request to the EMA. In September 2023, the CHMP gave a negative opinion on the conversion of the conditional marketing authorization to full marketing authorization of Translarna for the treatment of nmDMD and a negative opinion on the renewal of the existing conditional marketing authorization of Translarna for the treatment of nmDMD. On January 25, 2024, the CHMP issued a negative opinion for the renewal of the conditional marketing authorization following a re-examination procedure. In accordance with EMA regulations, the EC has 67 days to adopt the opinion. If the EC adopts the negative opinion, Translarna would no longer have marketing authorization in the member states of the EEA. Given the negative opinion from the CHMP, we believe that it is likely that the EC will refuse to renew the marketing authorization for Translarna. While we are exploring other potential mechanisms in which we may provide Translarna to nmDMD patients in the EEA, we may be unable to identify processes that are both possible within the regulatory frameworks of individual EEA countries and commercially viable. As such, there is substantial risk to our ability to maintain our conditional marketing authorization in the EEA and our ability to commercialize Translarna for the treatment of nmDMD in the EEA. If we are unable to renew our conditional marketing authorization in the EEA or we are unable to identify other potential mechanisms in which we may provide Translarna to nmDMD patients in the EEA, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna in the EEA, which would have a material adverse effect on our business, results of operations and financial condition. Additionally, the CHMP' s negative opinion for Translarna and potential loss of the Translarna marketing authorization in the EEA may influence regulatory entities in other jurisdictions in which Translarna has been approved to reassess such approvals. For example, certain countries reference or depend on the determination by the EMA when considering the grant of a marketing authorization. There is substantial risk that we would be unable to maintain our marketing authorizations in these countries in the event the EC decides not to renew or otherwise varies, suspends or withdraws our marketing authorization in the EEA. Even in countries where our marketing authorization is maintained, there may be an impact on pricing and reimbursement of Translarna within those countries. Any potential reassessments or scheduled renewals of our marketing authorizations or impacts to pricing and reimbursement may lead to additional regulatory costs, requirements to complete additional clinical trials, restrictions on or removal of our marketing authorizations or loss of a significant portion of our revenue for Translarna in other jurisdictions, which could have a material adverse effect on our business, results of operations and financial condition. If** we are unable to continue to execute our commercial strategy for our products, fail to obtain renewal of, or satisfy the conditions of our marketing authorization for our products, or if we experience significant delays in accomplishing such goals, our business will be materially harmed. We have invested a significant portion of our efforts and financial resources to bring our products to market through research and development, collaborations and acquisitions. Our ability to continue to generate product revenues will depend heavily on the successful commercialization of our products. If we do not successfully maintain our marketing authorizations for our products and obtain new marketing authorizations for our product candidates and new uses of our approved products, our ability to generate additional revenue will be jeopardized and, consequently, our business will be materially harmed **. Additionally, our ability to make our licensed 62products available within the relevant territories is largely dependent upon the maintenance of the marketing authorizations by the licensor** . The success of our products will depend on a number of additional factors, including the following: ● our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms on a timely basis, or at all; ● the timing, scope and outcome of commercial launches; ● the maintenance and expansion of a commercial infrastructure capable of supporting product sales, marketing and distribution; ● the implementation and maintenance of marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization; ● our ability to establish and maintain commercial manufacturing arrangements with third- party manufacturers; ● our ability or the ability of our third- party manufacturers to successfully produce commercial and clinical supply of drug on a timely basis sufficient to meet the needs of our commercial and clinical activities; ● successful identification of eligible patients; ● acceptance of the drug as a treatment for the approved indication by patients, the medical community and

third- party payors; ● effectively competing with other therapies; ● global trade policies; ● a continued acceptable safety profile of the drug; ● the costs, timing and outcome of post- marketing studies and trials required for our products ~~, including, with respect to Translarna, Study 041~~ ; ● protecting our rights in our intellectual property portfolio, obtaining and maintaining regulatory exclusivity and whether we are able to maintain market exclusivity periods under the Orphan Drug Act or equivalent protections in other jurisdictions; ● whether negative results from our clinical or pre- clinical trials of a product for one indication affect the perception of such product in another indication, including with respect to determinations by regulators, including the FDA and EMA, with respect to our ongoing or future regulatory submissions for marketing authorization of our products for any indication; ● whether, with respect to Translarna, we are able to continue to satisfy our obligations under, and maintain, the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit- risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label; ● whether, and within what timeframe, we are able to advance Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non- clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States; ● our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for our products on adequate terms; ● ● our ability to successfully prepare and advance regulatory submissions for marketing authorizations for our products in additional territories and for additional or expanded indications and whether and in what timeframe we may obtain such authorizations; ~~and65~~ **and** ● the ability and willingness of patients and healthcare professionals to access our products through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to continue to commercialize our products, either of which would have a material adverse effect on our business, results of operations and financial condition. ~~Delays~~ **63Delays** or failures in obtaining regulatory approval would prevent us from commercializing our product candidates in the applicable territory and our ability to generate revenue will be materially impaired. Moreover, should we need to conduct additional development work, other than those we have planned, we expect to incur significant costs, which may have a material adverse effect on our business and results of operations. There is significant risk that we will be unable to obtain approval for our product candidates on a timely basis or at all, and we may be required to perform additional clinical trials, non- clinical studies or CMC assessments or analyses at significant cost. Product development is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. This is especially true for rare and / or complicated diseases. A failure of one or more clinical or preclinical trials, or manufacturing development can occur at any stage. Preclinical and clinical studies may also reveal unfavorable product candidate characteristics, including safety concerns, or may not demonstrate product candidate efficacy. ~~In some instances, there~~ **There** can be significant variability in results between different clinical trials of the same product candidate due to numerous factors. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing authorization of their products. The approval process is also subject to the substantial discretion of regulatory authorities and the approval procedures vary among countries, can involve additional testing, and the time for approval may materially differ and be subject to administrative delays that we cannot control. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. In response to changes in the regulatory environment or requests from regulators, we may elect, or be obliged, to postpone a regulatory submission to include additional analyses, which could cause delays in getting our products to market and substantially increase our costs. Securing marketing authorization also requires the submission of information about the product manufacturing process to, and inspection or conduct of remote regulatory assessments of manufacturing facilities by, the regulatory authorities. Changes to manufacturers, product candidate formulation, manufacturing processes and other product candidate attributes, such as the method of delivery, during product candidate development may also require additional studies to demonstrate the comparability of the product candidate using prior processes, formulation, or manufacturers, or with the prior attributes, to the product candidate using new the processes, formulation, or manufacturers, or with the new attributes. For example, we have been seeking FDA approval for Translarna for nmDMD with the FDA since 2010 and the FDA has repeatedly disagreed with our interpretation of our results. In October 2017, the Office of Drug Evaluation I of the FDA issued a Complete Response Letter for the NDA, stating that it was unable to approve the application in its current form. In response, we filed a formal dispute resolution request with the Office of New Drugs of the FDA. In February 2018, the Office of New Drugs of the FDA denied our appeal of the Complete Response Letter. In its response, the Office of New Drugs recommended a possible path forward for the ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles. We followed the FDA' s recommendation and collected, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 did not meet its pre- specified primary endpoint. In June 2022, we announced top- line results from the placebo- controlled trial of Study 041. Following this announcement, we submitted a meeting request to the FDA to gain clarity on the regulatory pathway for a potential re- ~~66submission~~ **submission** of an NDA for Translarna. The FDA provided initial written feedback that Study 041 does not provide substantial evidence of effectiveness to support NDA re-submission. We **held a** ~~recently had an informal meeting with the FDA, during which we discussed the potential path to an~~

~~NDA re- submission for Translarna. Based on the meeting discussion, we plan to request an additional~~ Type C meeting with the FDA in the ~~near future~~ **fourth quarter of 2023** to ~~review~~ **discuss** the totality of **Translarna** data ~~collected to date~~ **. Based on this discussion** , ~~including dystrophin~~ **the FDA suggested we request a pre- submission Type C meeting to discuss the specific contents of** ~~and~~ **an** ~~other mechanistic data as well as additional analyses that could support the benefit of~~ **NDA resubmission based on results from Study 041 and from our international drug registry study for nmDMD patients receiving** Translarna. **This meeting is scheduled for March 2024.** ~~With 64~~**With** respect to Upstaza, in a late 2019 interaction with the FDA, the FDA requested additional information concerning the use of the commercial delivery system for Upstaza in young patients. In response to the FDA' s request, we provided additional information concerning the use of the commercial cannula for Upstaza in young patients. In October 2022, we held a ~~type~~ **Type** C meeting with the FDA to discuss the details of a potential submission package for Upstaza. At ~~such~~ **that** meeting, the FDA asked for additional bioanalytical data in support of comparability between the drug product used in the clinical studies and the commercial drug product. We ~~have~~ completed these analyses and provided the results to the FDA for review. **The FDA stated that the data that we provided were still not sufficient. However, the FDA also said that the available data from the ongoing clinical study in the United States assessing the safety of the drug delivery cannula for Upstaza could be used to support a BLA for accelerated approval based on biomarker data demonstrating a treatment- related increase in de novo dopamine production. At the FDA' s suggestion, we held a pre- BLA meeting in December 2023.** We expect to submit a BLA to the FDA ~~in~~ **for Upstaza for** the **treatment** ~~first half~~ of **AADC deficiency in March** ~~2023~~ **2024** . There is no guarantee that we will be able to achieve our milestones at all or within our anticipated timeframes, or that regulators may have additional questions to which we will need to respond. There is also substantial risk that the results of our future or current studies will not ultimately support the approval of a product candidate. **Regulators may also request additional studies, data and information, that we may need to develop and which were not originally planned for.** Any delays in obtaining regulatory approval, or if we never obtain regulatory approval, could have a material adverse effect on our business, financial condition and results of operations. We may use certain specialized pathways to develop our product candidates or to seek approval. We may not qualify for these pathways or such pathways may not ultimately speed the time to approval or result in product candidate approval. In the United States, we may pursue the accelerated approval pathway for certain of our product candidates, such as Translarna. However, the FDA may find that our product candidates do not qualify for accelerated approval. Moreover, even if we do ultimately receive accelerated approval, we would need to meet certain post approval requirements, such as completing a post- approval study confirming our product candidates' clinical benefit that may require substantial time, effort, and funds. **The** ~~Under a newly enacted law, the~~ FDA must specify the conditions for the required post approval studies, including enrollment targets, the study protocol, milestones, and target completion dates, by the time of approval and the FDA may require that the post- approval studies be commenced before the date of approval. If this study does not confirm the product' s clinical benefit or if the study is not conducted in accordance with the FDA' s requirements, it would be subject to the risk of expedited FDA withdrawal. Additional regulatory requirements also include the pre- submission of promotional materials to the FDA and potential restrictions, such as distribution restrictions, to assure the product' s safe use. In recent years, the accelerated approval pathway has come under significant FDA and public scrutiny. Accordingly, depending on the results of our studies, the FDA may be more conservative in granting accelerated approval or, if granted, may be more apt to withdrawal approval if clinical benefit is not confirmed. Due to these and other uncertainties, we are unable to estimate the timing or potential for product candidates for which we may use the accelerated approval pathway or the cost or effort required to receive FDA approval. Further, even if we receive accelerated approval, there is no guarantee that we would be able to maintain such approval. ~~For our gene therapy product candidates, we may pursue an exceptional circumstances marketing authorization from the EMA. If a product candidate is eligible for marketing authorization under exceptional circumstances, the authorization would be subject to a requirement for the applicant to implement specific procedures, in particular related to notification of the competent authorities of any safety issue. Such exceptional circumstance marketing authorizations are annually reassessed and after five years, the authorization may be renewed under exceptional circumstances for an unlimited period, or the EMA may decide, on justified grounds relating to pharmacovigilance, to proceed with one additional five- year renewal. If any product we have is approved under the exceptional circumstances process, there is no guarantee that we will be able to maintain such approval. Moreover, our product candidates may not be eligible for exceptional circumstances marketing authorization. 67If~~ we or our collaborators experience any of a number of possible unforeseen events in connection with clinical trials related to our products or our product candidates, maintenance of our existing marketing authorization for our products and any additional potential marketing authorization or commercialization of our products or our product candidates could be delayed or prevented. We or our collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing authorization or commercialize our products or our product candidates, including: ● clinical trials may produce negative or inconclusive results, regulators may disagree with our interpretation of results, our studies may fail to reach the necessary level of statistical significance, or we may not be able to demonstrate that our product candidates are safe, effective, or provide an advantage over current standard of care or other therapies; **65** ● our clinical trials may not meet their primary endpoints. For example, for Translarna, the primary efficacy endpoint in the intent to treat, or ITT, population did not achieve statistical significance in the Phase 2b trial (completed in 2009), Phase 3 trial in ACT DMD (completed in 2015), or Study 045 (completed in 2021); ● there may be flaws in our clinical trials' design that may not become apparent until the clinical trials are well advanced or regulators may not agree with the design of our studies or our analysis of the resulting data; ● clinical trial sites or enrolled patients **, as well as the resulting data,** may be negatively affected by outbreaks of **contagious disease, such as** COVID- 19 ~~or other outbreaks of contagious disease~~ , resulting in delays and disruptions in completing clinical trials, such as the delays we experienced in **2021 and 2022 in** enrolling **a** ~~our registration- directed~~ Phase 2 / 3 placebo- controlled trial of vatiquinone in children with mitochondrial disease associated seizures trial as some patients were unable or hesitant to travel to

clinical trial sites due to the COVID- 19 pandemic **. The exact impact of any contagious disease outbreak may not be fully known until the applicable trials are complete or are submitted to the applicable regulatory authorities** ; ● we may be unable to enroll a sufficient number of patients in our clinical trials, the number of patients required for clinical trials may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials, not comply with trial procedures, misrepresent their eligibility, or be lost to follow- up at a higher rate than we anticipate; ● we may enroll patients in foreign countries in which clinical sites may have less experience with studies or the disease at issue, or may use a different standard of care; regulatory authorities may not accept the data generated at foreign sites; ● 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 we may be required to engage in additional clinical trial site monitoring; ● regulators, institutional review boards, institutional biosafety committees, or independent ethics committees may not authorize us or our investigators to commence or continue a clinical trial, may require additional data or studies, or may require changes to our studies, including applications and protocols; ● we may be unable to engage trial sites and contract research organizations or they may withdraw from our studies; ● we, regulators, institutional review boards, institutional biosafety committees, or independent ethics committees may require the suspension or termination of studies for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks; ● the cost of clinical trials of our products or our product candidates may be greater than we anticipate or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of a marketing application; ● the supply or quality of our products or our product candidates or other materials necessary to conduct clinical trials of our products or our product candidates may be insufficient or inadequate; ● regulators may require us to perform additional or unanticipated studies, develop additional manufacturing information, or make changes to our manufacturing process to obtain approval; ● there may be changes in the applicable regulatory authorities' approval requirements, which may render our data insufficient to obtain marketing approval; ● the FDA or comparable regulatory authorities may disagree with our intended indications; ● regulators may fail to approve or subsequently find fault with the manufacturing processes or facilities for clinical and future commercial supplies; ● the FDA or comparable regulatory authorities may take longer than we anticipate to make a decision on our product candidates; ~~or68~~ **or** ● we may decide to abandon the development of a product candidate or development program. ~~These~~ **66These** risks may be increased for product candidates intended for the treatment of diseases for which there is little clinical experience, where we are using new endpoints or methodologies, or where the product candidates are new or novel. For example, there are no marketed therapies approved to treat the underlying cause of nmDMD and there is limited clinical trial experience with respect to drugs to treat nmDMD and other diseases that we are studying or have studied. As a result, the design and conduct of clinical trials for these diseases, particularly for drugs to address the underlying nonsense mutations causing these diseases in some subsets of patients, is subject to increased risk. Furthermore, the regulatory requirements regarding gene therapies are continually evolving and regulatory authorities have only approved a limited number of gene therapies. Moreover, because gene therapy products are a relatively new development, less is known about such products and product candidates and, accordingly there is an increased risk that such products may not perform as expected. Regulatory review agencies and the requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional or larger studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post- approval studies, limitations or restrictions. We may also experience increased risks to the extent that product candidates require a specialized delivery device or method. For example, Upstaza is administered directly to the putamen in the brain using stereotactic surgery, a brain surgery requiring significant skill and training. There is little experience with such surgeries being used to deliver drugs and for such surgeries being performed on children. We may need to train sufficient brain surgeons to perform the procedure properly, which may expose us to additional regulatory risks as our interactions with such healthcare providers must comply with all applicable laws and regulations. As a result, we will need to invest significant resources to ensure all personnel and contractors are adequately trained on these requirements and to monitor their conduct. Delivery of Upstaza to the putamen also requires certain medical devices, which may result in our product candidate being deemed to be a combination product by the FDA, requiring compliance with the FDA' s device regulations and collaboration with medical device manufacturers. Our product development costs will increase if we experience delays in testing or marketing authorizations, and we may not have sufficient funding to complete the testing and approval process for any of our product candidates. We may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our products and product candidates. We do not know whether any preclinical tests or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our products or our product candidates and allow our competitors to bring products to market before we do or impair our ability to successfully commercialize our products or our product candidates, and so may harm our business, results of operations and financial condition. Subgroup, retrospective, post- hoc, and certain statistical analyses may not be reliable and typically will not form the basis for regulatory approval. In the event that a study' s primary endpoint is not met, companies may undertake certain analyses to further understand the data and potential reasons for the study results, including retrospective, post- hoc, and subgroup analyses. Because these analyses are not pre- planned and studies may not be adequately designed for these analyses, they may not be reliable and typically will not form the basis for regulatory approval. For example, after determining that we did not achieve the primary efficacy endpoint with the pre- specified level of statistical significance in our completed ACT DMD and Phase 2b clinical trials of Translarna for the treatment of nmDMD, we performed subgroup, retrospective, and meta- analyses. We submitted these analyses to the FDA as part of our NDA, taking the position that the totality of clinical data from these trials support the clinical benefit of Translarna for the treatment of nmDMD. The FDA, however, did not agree that these analyses supported approval. Some of our favorable statistical data from these trials also

are based on nominal p- values. Nominal p- values are subject to certain limitations, and which, because of these limitations, regulatory authorities typically give less weight to nominal p- values, compared to regular p- values. For example, the p- values in ACT DMD for change from baseline at week 48 in the 6- minute walk test, or 6MWT (which we also refer to as 6- minute walk distance, or 6MWD) and each secondary end ~~69point --~~ **point** timed function test were nominal p- values. The FDA found that certain post- hoc adjustments, our retrospective analyses and our reliance on nominal p- values for some of our statistical data did not support approval. ~~An~~ **67An** unfavorable view of our data and analyses by regulatory authorities has and could continue to negatively impact our ability to obtain or maintain marketing authorizations, which would have a material adverse effect on our revenue and would materially harm our business, financial results and results of operations. If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented. We may not be able to initiate or continue clinical trials for our product candidates, including clinical trials due to the inability to enroll a sufficient number of patients. Patient enrollment is affected a number of factors including: ● the size of the patient population (many of our studies concern rare conditions with small patient populations); ● the availability of approved treatments; ● severity of the disease under investigation; ● eligibility criteria for the study in question; ● perceived benefits and risks of the product candidate under study; ● disruptions caused by and the willingness of patients to enroll in a clinical trial during outbreaks of **contagious disease, such as** COVID- 19; ● efforts to facilitate timely enrollment in clinical trials; ● patient referral practices of physicians; ● competition from other clinical trials; ● the ability to monitor patients adequately during and after treatment; and ● proximity and availability of clinical trial sites for prospective patients. For example, we previously experienced delays in **2021 and 2022** enrolling **a** ~~our registration- directed~~ Phase 2 / 3 trial of vatiquinone in children with mitochondrial disease associated seizures as some patients were unable or hesitant to travel to clinical trial sites due to the COVID- 19 pandemic. ~~We anticipate results from the Phase 2 / 3 trial to be available in the second quarter of 2023.~~ Enrollment delays in our clinical trials may result in increased development costs for our product candidates. Our inability to enroll, timely or at all, a sufficient number of patients in our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. If serious adverse side effects are identified during the development of any product candidate or for any product for which we have or may obtain marketing approval, we may need to abandon or limit our development and / or marketing of that product or product candidate. If our products or our product candidates are associated with undesirable side effects or have characteristics that are unexpected, regulatory authorities, institutional review boards, institutional biosafety committees, or independent ethics committees may place our studies on clinical hold, withdraw or suspend study approvals, or require that we modify our protocols. We may also need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a benefit- risk perspective. Adverse events or side effects may also result in study recruitment challenges, marketing authorization denial, limitations on the indicated use of a product, the inclusion of warnings, contraindications, or precautions on the label of any approved products, or significant conditions imposed on any approval, including the requirement of a risk evaluation and mitigation strategies, or REMS, costly post- marketing studies or clinical trials and surveillance to monitor the safety of the product. Adverse effects may also prevent the adoption of a product, if it is approved. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development of the compound. Furthermore, we may be sued and held liable for harm caused by our products to patients as a result of the identification of undesirable side effects, which may cause reputational harm. ~~70For --~~ **For** example, although we did not observe a pattern of liver enzyme elevations in our Phase 2 or Phase 3 clinical trials of Translarna, we did observe modest elevations of liver enzymes in some subjects in one of our Phase 1 clinical trials. These elevated enzyme levels did not require cessation of Translarna administration, and enzyme levels typically normalized ~~after~~ **68after** completion of the treatment phase. We did not observe any increases in bilirubin, which can be associated with serious harm to the liver, in the Phase 1 clinical trial. In addition, in Study 009, our first Phase 3 clinical trial of Translarna for the treatment of nmCF, five adverse events in the Translarna arm of the trial that involved the renal system led to discontinuation. As compared to the placebo group, the Translarna treatment arm also had a higher incidence of adverse events of creatinine elevations, which can be an indication of impaired kidney function. In the Translarna treatment arm, more severe clinically meaningful creatinine elevations were reported in conjunction with cystic fibrosis pulmonary exacerbations. These creatinine elevations were associated with concomitant treatment with antibiotics associated with impaired kidney functions, such as aminoglycosides or vancomycin. This led to the subsequent prohibition of concomitant use of Translarna and these antibiotics, which was successful in addressing this issue in the clinical trial. The risk of finding adverse side effects may be particularly heightened in the case of gene therapies. For instance, new gene copies may produce too much or too little of the desired protein or RNA, or the production of the desired protein or RNA may change over time. Because the treatment is irreversible, there may be challenges in managing side effects. Adverse effects would not be able to be reversed or relieved by stopping dosing and might require us to develop additional clinical safety procedures. Furthermore, new gene copies may disrupt other normal biological molecules and processes. Adverse side effects may also be experienced by patients as a result of the process for administering the therapy or related procedures. There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia, immune- and complement- mediated responses, and death seen in other trials using other vectors. While new recombinant vectors have been developed to potentially reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. For instance, possible adverse side effects that could occur include an immunologic or complement- mediated reactions early after administration which, could substantially limit the effectiveness of the treatment. Depending on the vector, additional manufacturing, clinical, and preclinical testing may be required, as well as additional analyses, assessments, and potential long- term patient and clinical study subject monitoring and sample testing and associated regulatory reporting. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not

ultimately attributable to the relevant product candidates, and the resulting publicity, could further adversely impact our product candidates in the form of increased government regulation, unfavorable public perception, potential regulatory delays, stricter labeling requirements, and a decrease in demand. If, following approval, we or others identify previously unknown side effects, if such side- effects are severe, or if known side effects are more frequent or severe than in the past then our marketing authorizations may be restricted or withdrawn, changes may be required to the product' s label, sales may be adversely impacted, we may be required to undertake additional studies or trials, and government investigations or litigation, including product liability claims, may be brought against us. Additionally, if the safety warnings in our product labels are not followed, adverse medical situations in patients may arise, resulting in negative publicity and potential lawsuits. Any of these occurrences would limit or prevent us from commercializing our products, which would have a material adverse effect on our business, financial results and operations. Certain of our products and product candidates ~~, such as our gene therapies and other biologic product candidates,~~ may be difficult to produce, presenting manufacturing challenges that may delay product development and regulatory approval. Manufacturers of pharmaceutical products must comply with strictly enforced manufacturing and quality requirements, including cGMP requirements, state and federal regulations, as well as ex- U. S. requirements when applicable. These may be particularly difficult to meet for complex products such as biologic and gene therapy products. Any failure to meet the applicable manufacturing and quality requirements could lead to a delay or interruption in development programs, delays in receiving regulatory approval, and consequences should we receive marketing approval. ~~71The~~ -- **The** manufacture of biologic and gene therapy products is technically complex, requires extreme precision to meet specification requirements and necessitates substantial expertise and capital investment. Production difficulties caused by unforeseen events, even if seemingly minimal, may delay the availability of material for clinical studies and commercial ~~product~~ **69product** . For example, given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our ability to produce our gene therapy product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage. In addition, gene therapy products have only in limited cases been manufactured at scales sufficient for pivotal trials and commercialization. Few pharmaceutical contract manufacturers specialize in gene therapy products and those that do are still developing appropriate processes, controls and facilities for large- scale production. While we believe that there are alternative sources of supply that can satisfy our clinical and commercial requirements **for Upstaza** , we cannot be certain that we will be able to identify and establish relationships with such sources, if necessary, in a timely manner or at all, and what the terms and costs of such new arrangements would be, or that such alternative suppliers would be able to supply our potential commercial needs. To the extent that we decide to manufacture our own clinical and commercial supply **of Upstaza** as an alternative source of supply, there is no guarantee that we will be able to cost effectively produce sufficient quantities of our program material. Any switch from our current manufacturer would result in a significant delay, would require regulatory authority approval, and cause material additional costs. Furthermore, some of the raw materials and other components required in our manufacturing process are derived from diverse biologic sources that may be difficult to procure and may be subject to contamination or recall. Any material shortage, supply chain disruption, contamination recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the production and commercialization of products. **We have** ~~In 2021, we began cGMP~~ manufacturing **services related to the production** of ~~clinical material~~ **plasmid DNA and AAV vectors for gene therapy applications for external customers** at ~~the~~ **our** Hopewell Facility ~~for certain of our gene therapy product candidates other than Upstaza~~ . We ~~still rely on third- party manufacturers to complete product testing for all of our gene therapy product candidates that we manufacture at the Hopewell Facility as well as to provide sufficient quantities of certain program materials that we have not yet transitioned to the Hopewell Facility. To the extent we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers. With respect to the Hopewell Facility, we have limited experience conducting our own manufacturing and could encounter problems and delays. The Hopewell Facility requires substantial investment and significant expertise, and our management devotes substantial time to its operation. There is substantial competition for skilled personnel within gene therapy manufacturing and we may not be able to attract and retain these personnel on acceptable terms. Moreover, operating a manufacturing facility may cost more than we currently anticipate. If we experience any problems or delays with the Hopewell Facility, we may need to rely on contract manufacturers for the manufacturing of program materials that we intended to produce ourselves, which may not be available or on acceptable terms. Additionally, we~~ have limited experience producing plasmid DNA and AAV vectors for third party customers ~~, and we have yet to manufacture cGMP gene therapy product materials for our own clinical trials or commercialization~~ . If we are unable to manufacture these product materials to the required specifications **and regulatory requirements** for the third parties we contract with, our business, financial condition, and results of operations could be materially adversely affected and we may become subject to regulatory or contractual actions, may need to expend significant time and costs to remedy issues, and we may forgo sales, incur liabilities or lose customers, which would materially adversely affect our business, financial condition and results of operations. Finally, we and our third party manufacturers may experience any number of unforeseen issues, unforeseen delays, including equipment failure, labor shortages, natural disasters, power failures, transportation difficulties, quality control or other issues, including those resulting from compliance with regulatory requirements, as further described in these risks, that could prevent us from realizing the intended benefits of our manufacturing strategy. ~~72The marketing authorization granted by the European Commission for Translarna for the treatment of nmDMD is limited to ambulatory patients aged two years and older located in the EEA, which significantly limits an already small treatable patient population, which reduces our commercial opportunity and is also subject to annual reassessment of the benefit- risk balance by the EMA as well as the specific obligation to conduct Study 041, and may be varied, suspended or withdrawn by the European Commission if we fail to satisfy those requirements. The marketing label for Translarna approved by the European Commission is limited to ambulatory nmDMD patients aged two years and older who have been identified through genetic testing as having a nonsense mutation in the dystrophin gene. Prevalence estimates for rare~~

~~diseases are uncertain due to the uncertainties associated with the methodologies used to derive estimates, such as epidemiology assumptions. It can take many years of experience in rare disease market places before prevalence becomes well characterized. Our estimates of both the number of people who have DMD caused by a nonsense mutation, as well as the subset of people with nmDMD who are ambulatory and at least two years old, are based on our beliefs and estimates derived from a variety of sources and may prove to be either incorrect or subject to additional refinement or characterization on a country specific basis over the coming years. If the market opportunities for Translarna for the treatment of nmDMD are smaller than we believe they are, our business and anticipated revenues will be negatively impacted. If we decide to seek to expand the approved product label of Translarna for the treatment of nmDMD in the future, the timing of, and our ability to generate, the necessary data or results required to obtain expanded regulatory approval is currently uncertain. Given the small number of patients who have nmDMD, and the smaller number of patients who meet the criteria for treatment under our current marketing authorization, our commercial opportunity is limited. It is critical to the commercial success of Translarna for nmDMD that we successfully identify and treat these patients. In order to continue to generate revenue from Translarna, we must maintain our current marketing authorizations in a number of countries and we also may need to receive or maintain marketing authorizations in other territories. The marketing authorization in the EEA is conditional and subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit- risk balance of the authorization, which we refer to as the annual EMA reassessment. In June 2022, the European Commission renewed our marketing authorization, making it effective, unless extended, through August 5, 2023. This marketing authorization is further subject to a specific obligation to conduct and submit the results of Study 041. In June 2022, we announced top- line results from the placebo- controlled trial of Study 041. In September 2022, we submitted a Type II variation to the EMA to support conversion of the conditional marketing authorization for Translarna to a standard marketing authorization, which included a report on the placebo- controlled trial of Study 041 and data from the open- label extension. We expect an opinion from the Committee for Medicinal Products for Human Use in the first half of 2023. If the EMA determines in any annual renewal cycle that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with any conditions that have been or may be placed on the marketing authorization, the European Commission could, at the EMA' s recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require the imposition of other conditions or restrictions. As such, there is ongoing risk to our ability to maintain our marketing authorization in the EEA. If we are unable to renew our marketing authorization in the EEA during any annual renewal cycle, or if our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program, and in all territories, which would have a material adverse effect on our business, results of operations and financial condition.~~ Any of our products or any other product candidate that receives marketing authorization ~~, if any,~~ may fail to achieve the degree of market acceptance by physicians, patients, third- party payors and others in the medical community necessary for commercial success. Even if we are successful in obtaining and maintaining marketing authorizations, our products may not gain sufficient market acceptance by physicians, patients, third- party payors and others in the medical community. Third- party payors may require prior authorizations or failure on another type of treatment before covering a particular drug, particularly with respect to higher- priced drugs. Decreases in third- party reimbursement for a product or a decision by a third- party payor to not cover a product could reduce physician usage of the product. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenues or any profits from operations. ~~73The~~ **The** degree of market acceptance of our products or product candidates, if approved for commercial sale, will depend on a number of factors, including: ● the efficacy and potential advantages, as well as cost effectiveness compared to alternative treatments; ● the prevalence and severity of any side effects, as well as perceived safety; ● limitations or warnings contained in, as well as permitted claims based on the product' s FDA- approved labeling; ● distribution and use restrictions imposed by the FDA or which we voluntarily implement; ● the ability to offer our products or product candidates for sale at competitive prices; **70** ● the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies. For example, gene therapy remains a novel technology, must be administered directly to the brain via a surgery and public perception may be influenced by claims that gene therapy is unsafe, which may cause gene therapy to not gain acceptance by the public or the medical community; ● the convenience and ease of administration compared to alternative treatments; ● the strength of marketing and distribution support; ● sufficient third- party coverage or reimbursement and, where applicable, our ability to obtain pricing approvals which is separate from the marketing authorization process; ● adverse publicity about our and our competitors' products or product candidates or favorable publicity about competitive products or product candidates. For example, earlier gene therapy trials conducted by other organizations have led to several well- publicized adverse events, including cases of leukemia, immune- and complement- mediated adverse events, and death seen in other such organizations' trials using vectors; ● the results of studies of the product in other indications or similar products; and ● any restrictions on concomitant use of other medications. Obtaining coverage and reimbursement for a product from third- party payers is a time- consuming and costly process. Failure to obtain adequate reimbursement may significantly impact the adoption and sale of products. Market acceptance and obtaining reimbursement coverage may be particularly challenging in the case of gene therapies, where the cost of a single administration may be substantial and adequate coverage and reimbursement will be essential for patients to afford the treatment. Payors may require us to provide supporting scientific, clinical and cost- effectiveness data, which we may not be able to provide. Moreover, ethical, social and legal concerns about certain treatments, such as gene therapy, could result in additional regulations restricting or prohibiting sale of our products. In the United States, third- party payers, including government payers such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. Expensive specialty drugs in particular are often subject to restriction. The Medicare and Medicaid programs increasingly are used as models for how private payers and government payers develop their coverage and reimbursement policies. We cannot

be assured that Medicare or Medicaid will cover our product candidates that may be approved or provide reimbursement without restriction and at adequate levels to realize a sufficient return on our investment. Our rebate payments may increase or our prices be adjusted under value- based purchasing arrangements based on evidence- based measures or outcomes- based measures for a patient or beneficiary based on use of our drug. Moreover, reimbursement agencies in the EU may be more conservative than CMS. It is difficult to predict what third- party payers will decide with respect to the coverage and reimbursement for our products for which we obtain marketing approval. Additionally, within Europe, each country has its own reimbursement regime employing various health technology assessment approaches to assess the cost- effectiveness of the product (**for example,** in the United Kingdom a HTA assessment is conducted by NICE) which may significantly affect the effective access to the market. Our ability to negotiate, secure and maintain third- party coverage and reimbursement may also be affected by political, economic and regulatory developments. Governments continue to impose cost containment measures, and third- party payors are increasingly challenging prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. These and other similar developments could significantly limit the degree of market acceptance of our products or any of our other product candidates that receive marketing authorization. ~~74If~~ **If** we are unable to establish or maintain sales, marketing and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products or product candidates, we may not be successful in our continuing efforts to commercialize our products or any other product candidate if and when they are approved. Our ongoing commercial strategy for our products and any other product candidate that may receive marketing authorization involves the development of a commercial infrastructure that spans multiple jurisdictions and is heavily dependent upon our ability to continue to build an infrastructure that is capable of implementing our global commercial strategy. The establishment and development of our commercial infrastructure will continue to be expensive and time consuming, and we may not be able to develop our commercial organizations in all intended territories, including in the United States, in a timely manner or at all. Doing so will require a high degree of coordination and compliance with laws and regulations in numerous territories, including restrictions on advertising practices, enforcement of intellectual property ~~rights~~ **71rights** , restrictions on pricing or discounts, transparency laws and regulations, and unexpected changes in regulatory requirements and tariffs. If we are unable to effectively coordinate such activities or comply with such laws and regulations, our ability to commercialize our products or any other product candidates that may receive marketing authorization will be adversely affected. If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue consistent with our expectations and may not become profitable. There are risks involved with establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training an internal commercial team is expensive and time consuming and could delay commercialization efforts. If a commercial launch for any product or product candidate for which we recruit a commercial team and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition such personnel. The arrangements that we have entered into, or may enter into, with third parties to perform sales and marketing services will generate lower product revenues or profitability of product revenues to us than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our products or product candidates. Factors that may materially affect our efforts to commercialize our products include: ● our ability to recruit, train and retain adequate numbers of effective sales and marketing personnel; ● our ability to monitor the legal and regulatory compliance of sales and marketing personnel; ● an inability to secure adequate coverage and reimbursement by government and private health plans; ● reduced realization on government sales from mandatory discounts, rebates and fees, and from price concessions to private health plans and pharmacy benefit managers necessitated by competition for access to managed formularies; ● the clinical indications for which the products are approved and the claims that we may make for the products; ● limitations or warnings, including distribution or use restrictions, contained in the products' approved labeling; ● any distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan; ● liability for sales or marketing personnel who fail to comply with the applicable legal and regulatory requirements; ● our ability to implement third- party marketing and distribution relationships on favorable terms, or at all, in territories where we do not pursue direct commercialization; ● the ability of our commercial team to obtain access to or persuade adequate numbers of physicians to prescribe our current or any future products; ~~75~~ ● the lack of complementary products to be offered by our commercial team, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and ● unforeseen costs and expenses associated with creating an independent commercial organization. Any of these factors, individually or as a group, if not resolved in a favorable manner may have a material adverse effect on our business and results of operations. Similar risks apply in those territories where any of our products are available on a reimbursed basis under an EAP program. ~~A~~ **72A** substantial portion of our commercial sales currently occurs in territories outside of the United States which subjects us to additional business risks that could adversely affect our revenue and results of operations. We commercialize Translarna, Upstaza, Tegsedi and Waylivra outside of the United States. We have operations in multiple European countries, Latin America and other territories. We expect that we will continue to expand our international operations in the future, including in emerging growth markets, pending successful completion of the applicable regulatory processes. International operations inherently subject us to a number of risks and uncertainties, including: ● political, regulatory, compliance and economic developments that could restrict our ability to manufacture, market and sell our products, including the Russia- Ukraine conflict and related sanctions that have been imposed by various countries in response thereto; ● financial

risks such as longer payment cycles, difficulty collecting accounts receivable, potentially high inflation rates **, sustained high interest rates** and exposure to fluctuations in foreign currency exchange rates; ● difficulty in staffing and managing international operations; ● ~~various effects and responsive measures relating to COVID- 19 outbreaks; ●~~ potentially negative consequences from changes in or interpretations of tax laws; ● changes in international medical reimbursement policies and programs; ● unexpected changes in healthcare policies of ex- U. S. jurisdictions; ● trade protection measures, including import or export licensing requirements and tariffs; ● our ability to develop relationships with qualified local distributors and trading companies; ● political and economic instability in particular ex- U. S. economies and markets, in particular in emerging markets, for example in Brazil; ● diminished protection of intellectual property in some countries outside of the United States; ● differing labor regulations and business practices; ~~and~~ ● regulatory and compliance risks that relate to maintaining accurate information and control over sales and distributors' and service providers' activities that may fall within the purview of the Foreign Corrupt Practices Act, UK Bribery Act or similar local regulation ~~.~~**; and ● various effects and responsive measures relating to outbreaks of contagious disease, such as COVID- 19;** For example, the Brazilian Ministry of Health **has previously** ~~is continuing to experience~~ **experienced** significant administrative delays processing centralized group purchase orders. Almost all of our product revenue for Translarna in Brazil is attributable to such purchase orders. These centralized group purchase order delays have caused, and may continue to cause, fluctuations in our ability to generate revenue in Brazil. In addition, some countries in which a product candidate is not approved allow patients access to the product candidate through other legal mechanisms, including court intervention or EAP programs, if the product is approved in another jurisdiction. The price that is ultimately approved by governmental authorities in any country pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under such legal mechanisms and we may become obligated to repay such excess amount. Some of the countries in which our products are available for sale are in emerging markets. Some countries within emerging markets, including those in Latin America, may be especially vulnerable to periods of global or regional financial instability or may have very limited resources to spend on. We also may be required to increase our reliance on third- party agents within less developed markets. In addition, many emerging market countries have currencies that fluctuate substantially and if such currencies devalue and we cannot offset the devaluations, our financial performance within such countries could be adversely affected. ~~76Furthermore~~ -- **Furthermore** , in some countries, including Brazil and Russia, orders for named patient sales may be for multiple months of therapy, which can lead to an unevenness in orders which could result in significant fluctuations in quarterly net product sales. Other factors may also contribute to fluctuations in quarterly net product sales including a product' s availability in any particular territory, government actions, economic pressures, political unrest and other factors. Net product sales are impacted by factors such as the timing of decisions by regulatory authorities and our ability to successfully negotiate favorable pricing and reimbursement processes on a timely basis in the countries in which we have or may obtain regulatory approval, including the United States, EEA and other territories. ~~Any~~ **73Any** of these factors may, individually or as a group, have a material adverse effect on our business and results of operations. As we continue to expand our existing international operations, we may encounter new risks. Laws and regulations governing export restrictions and economic sanctions may preclude us from developing and selling certain products, generating revenue from such products, and manufacturing certain materials outside of the United States. Many countries, including the United States, restrict the export or import of products to or from certain countries through, for example, bans, sanction programs, and boycotts. Such restrictions may preclude us from supplying products or generating revenue in certain countries or may require an export license prior to the export of the controlled item. Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non- U. S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Furthermore, if we, or third parties acting on our behalf, do not comply with these restrictions, we may be subject to substantial civil and criminal penalties and suspension or debarment from government contracting. Our activities outside of the United States, require that we dedicate resources to comply with these laws. Many of our customers and suppliers are ex- U. S. entities or have significant ex- U. S. operations. Although these restrictions have not affected our operations in the past, there is a risk that they could do so in the future as additional geographic regions and entities may become subject to such restrictions. The imposition of new or additional economic and trade sanctions against our major customers or suppliers or financial counterparties or intermediaries could result in our inability to sell to, and generate revenue from such customers or purchase materials from such suppliers. For example, we make sales of Translarna through a distributor to the Ministry of Health of the Russian Federation to access Russian nmDMD patients. Our ability to generate and realize revenue in Russia may be materially and adversely impacted as many countries, including the United States, have imposed and may continue to consider imposing additional enhanced export controls on certain products and sanctions on certain industry sectors and parties in Russia in connection with the Russia- Ukraine conflict. We also contract with government- owned hospitals and third- party manufacturers located in China, which has recently been involved in political conflict with the United States. This conflict has increased the likelihood of restrictions that could materially and adversely affect our clinical trial sites located in China, our ability to obtain certain supplies, our ability to manufacture certain product candidates and our ability to potentially commercialize products in China. If our activities are affected because of these or other such restrictions, sanctions, or controls, our business, financial condition and results of operations could be materially and adversely affected. As a result of restrictive export laws, our customers may also seek to obtain a greater supply of similar or substitute products from our competitors that are not subject to these restrictions, which could materially and adversely affect our business, financial condition and results of operations. We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do. The development and commercialization of new drug products is highly competitive. We face competition with respect to our current products and product candidates and any products we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology

companies worldwide. Other gene therapy companies may in the future decide to utilize existing technologies to address unmet needs that could potentially compete with our product candidates. There is currently no marketed therapy **for nmDMD** , other than Translarna in the EEA ~~, which~~ **. Santhera Pharmaceuticals** has received approval ~~for the treatment of~~ **Agramee (vamorolone) in** the ~~underlying cause of~~ **United States for** ~~nmDMD~~ -- **DMD patients ages 2 and up and in the EU and United Kingdom for patients ages 4 years and older** . Sarepta ~~recently~~ **Therapeutics has received approval of Elevidys for DMD patients 4 to 5 years of age with a confirmed mutation in the " DMD gene " in the United States (Accelerated Approval granted with Full Approval pending) and United Arab Emirates and Qatar. Sarepta Therapeutics has also** received approval in the United States for two treatments (Exondys ~~7751~~ **51** (eteplirsen) and Vyondys 53 (golodirsen)) addressing the underlying cause of disease for different mutations in the DMD gene. Additionally, the FDA granted accelerated approval to Viltepso (viltolarsen) from NS Pharma for the treatment of DMD in patients with exon 53 skipping and Sarepta (Casimersen (SRP 4045) for the treatment of DMD in patients with exon 45 skipping. Viltepso (viltolarsen) from NS Pharma is also approved in Japan. Other biopharmaceutical companies are developing treatments ~~for~~ **addressing** the underlying cause of disease for ~~different~~ **74different** mutations in the DMD gene **, including, Dyne Therapeutics (DYNE- 251), Wave Life Sciences (WVE- N53)** , Daiichi Sankyo (DS ~~-~~5141 **)**), Nippon Shinyaku (Viltolarsen (NS ~~-~~065 / NCNP ~~-~~01) and NS ~~-~~089 / NCNP ~~-~~02 **)**), and Astellas (AT ~~-~~702). **Additionally,** ~~Other~~ **other** pharmaceutical companies are developing micro dystrophin gene therapies for patients with DMD regardless of genotype, including Pfizer (PF ~~-~~06939926) ~~,~~ **and** Solid Biosciences (SGT ~~-~~ 001) ~~and Sarepta (SRP- 9001), whose gene therapy has been submitted for accelerated approval to the FDA~~ . Although the FDA has not approved a corticosteroid specifically for DMD in the United States other than Emflaza, we face competition in the ~~U. S.~~ **United States in the** DMD market from prednisone / prednisolone, which, while not approved for DMD in the United States, is generically available and has been prescribed off label for DMD patients. ~~ReveraGen BioPharma and~~ Santhera ~~are developing a glucocorticoid antagonist~~ **has received approval of Agramee** (vamorolone) **, in the United States** for DMD patients **ages 2** ~~. An NDA for vamorolone has been submitted to~~ and **up** ~~accepted by the FDA,~~ and **in** the **European Union and United Kingdom** ~~Prescription Drug User Fee Act, or~~ **for** ~~PDUFA, date for a decision by~~ **patients ages 4 years and older. With** the ~~FDA is October 26,~~ **expiration of Emflaza' s orphan exclusivity for treatment of DMD in patients five years and older in February** ~~2023~~ **2024 , we expect to face competition from generic versions of Emflaza for this indication** . Currently, no other treatment options are available for the underlying cause of AADC deficiency. Additionally, we are not aware of any late-stage development product candidates for AADC deficiency. There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of Tegsedi and Waylivra. For example, **Ionis is developing Olezarsen for the treatment of FCS. Additionally,** Waylivra ~~for FCS~~ faces competition from ~~drugs like~~ Myalept (metreleptin) ~~. Myalept,~~ produced by ~~Novelion Therapeutics~~ **Chesi Farmaceutica** , Inc., **which** is currently approved **in Brazil** for use in generalized lipodystrophy patients. ~~Additionally, Ionis is developing AKCEA- APOCIII- LRx for the treatment of FCS. Currently, no other treatment options are available for the underlying cause of FPL. Additionally, we are not aware of any late- stage development product candidates for FPL.~~ Tegsedi ~~also~~ faces competition from drugs like Onpattro (patisiran) ~~,~~ which was launched by Alnylam **Pharmaceuticals** in the United States in 2018 and received approval in Brazil for the treatment of hATTR amyloidosis in 2020 as **was** well as AMVUTTRA (vutrisiran) which Alnylam **Pharmaceuticals** received approval for in the United States and Brazil in 2022 for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Vyndaqel (~~tafamidis~~ **tafamids** meglumine) and Vyndamax (tafamidis) are commercialized in the United States, EU and some ~~other~~ countries in Latin America by Pfizer. Other companies are also ~~pursing~~ **pursuing** product candidates for the treatment of ATTR Amyloidosis with polyneuropathy including BridgeBio Pharma (AG ~~-~~10 **), Intellia Therapeutics (NTLA2001**), Proclara Biosciences (NPT ~~-~~189 ~~), Prothena (PRK- 004~~) and SOM Biotech (tolcapone). **For** ~~Further, Tegsedi and~~ Waylivra ~~are delivered~~ **, Ionis is developing Olezarsen for the treatment of FCS. Waylivra also faces competition from Myalept, (metreleptin) produced** by ~~injection~~ **Cheisi Farmaceutica** , ~~which may render them less attractive to~~ **Inc., currently approved in Brazil for use in generalized lipodystrophy** patients ~~than non- injectable products offered by our current or future competitors. If Tegsedi or Waylivra cannot compete effectively with these and other products with common or similar indications, we may not be able to generate substantial revenue from our product sales~~ . Evrysdi, an orally bioavailable treatment, faces competition from treatments that are not orally bioavailable, including Spinraza (nusinersen), a drug developed by Ionis and marketed by Biogen, which **is** ~~has received FDA approval~~ **approved** to treat SMA and Zolgensma (onasemnogene abeparvovec), a gene therapy drug developed by AveXis, Inc., (acquired by Novartis in 2018), which is approved in the United States and Japan for the treatment of SMA in patients under 2 years of age and in Europe for babies and young children who weigh up to 21 kilograms **. Novartis is also developing OAV- 101, an intrathecal administration of Zolgensma, for SMA patients ages ≥ 2 to < 18 years of age. Biogen is developing a higher dose regimen of nusinersen with potential for improved efficacy and evaluating an implantable medical device to enable subcutaneous delivery of nusinersen** . Other companies are also pursuing product candidates for the treatment of SMA, including ~~Kowa (sodium valproate), Catalyst Pharmaceuticals (amifampridine),~~ Scholar Rock (**apitegromab,** SRK ~~-~~ 015 **), Biohaven (Taldefgrobep alfa**), Roche Pharmaceuticals (**RO-** ~~RO7204239~~ -- **7204239 / GYM- 329**) ~~and Cytokinetics~~ **, Biogen / Ionis** (~~reldesemtiv~~ **BIIB- 115 / ION-306**) ~~.~~ **and NMD Pharma (NMD- 670)** . For additional discussion regarding the competition we face with respect to our current product candidates, see " Item 1. Business- Competition. " Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are marketing or developing or that would render our products or product candidates obsolete or non- competitive. Our competitors may also obtain marketing authorization for their products more rapidly than we may obtain approval for our ~~78products~~ -- **products** and product candidates, which could result in our competitors establishing a strong market position before we are able to enter the market. We believe that many competitors are attempting to develop therapeutics for the target indications of our products and product candidates, including academic institutions, government agencies, public and private research organizations, large pharmaceutical companies and smaller more

focused companies. ~~Many~~ **75Many** of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to or necessary for our programs. Our products or product candidates may become subject to unfavorable pricing regulations, third- party reimbursement practices or healthcare reform initiatives, which would harm our business. We may not obtain adequate coverage or reimbursement for our products, or we may be required to sell our products at an unsatisfactory price. In addition, obtaining pricing, coverage and reimbursement approvals can be a time consuming and expensive process. Our business would be materially adversely affected if we do not receive these approvals on a timely basis. The regulations and practices that govern marketing authorizations, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries, including almost all of the member states of the EEA, require approval of the sale (list) price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some ex- U. S. markets, including the European market, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing authorization for a product in a particular country, but then be subject to price regulations, in some countries at national as well as regional levels, that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more products or other product candidates, even following marketing authorization. Our ability to successfully commercialize our products or product candidates that may receive marketing authorization will depend in large part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, managed healthcare organizations and other third- party payors and organizations. Government authorities and other third- party payors, such as private health insurers and managed healthcare organizations, decide which medications they will pay for and establish reimbursement conditions and rates. A primary trend in the EU and U. S. healthcare industries and elsewhere is cost containment. Government authorities, including the United States government and state legislatures, and other third- party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Prices at which our products are reimbursed can be subject to challenge, reduction or denial by the government and other payers. Increasingly, third- party payors are requiring that drug companies provide them with discounts off the products' sale (list) prices and are challenging the prices manufacturers charge for medical products. We cannot be sure that coverage will be available for any product or product candidate that we may commercialize and, if coverage is available, the level of reimbursement is also uncertain. Reimbursement levels may impact the demand for, or the price of, any product or product candidate for which we obtain marketing authorization. Obtaining reimbursement for our products has been and is expected to continue to be, particularly difficult due to price considerations typically associated with drugs that are developed to treat conditions that affect a small ~~79population~~ -- **population** of patients. In addition, third- party payors are likely to impose strict requirements for reimbursement of a higher priced drug, such as prior authorization and the requirement to try other therapies first, or high co- payments which can result in patient rejection. Decreases in third- party reimbursement for a product or a decision by a third- party payor to not cover a product could reduce physician usage of the product. If reimbursement is not available or is available only on a limited basis, we may not be able to successfully commercialize any product or product candidate for which we have obtained or may obtain marketing authorization. ~~There~~ **76There** may be significant delays in obtaining coverage for newly approved drugs, and coverage may be more limited than the drug' s approved indications as determined by the applicable regulatory authority. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent, and programs intended to provide patient assistance until coverage is established can be very costly **and limited in duration by law** . Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, and may be incorporated into existing payments for other services. Further, coverage policies and third- party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws, enforcement policies or administrative determinations with respect to the importation of drugs into the United States from other countries where they may be sold at lower prices. In the United States, third- party payors include federal healthcare programs, such as Medicare, Medicaid, TRICARE, and Veterans Health Administration programs; managed care providers, private health insurers and other organizations. Several of the U. S. federal healthcare programs establish ceiling prices or require that drug manufacturers extend discounts or pay rebates to certain programs in order for their products to be covered and reimbursed. For example, the Medicaid Drug Rebate Program requires pharmaceutical manufacturers of covered outpatient drugs to enter into and have in effect a national rebate agreement with the federal government as a condition for coverage of the manufacturer' s covered outpatient drug (s) by state Medicaid programs. The amount of the rebate for each product is based on a statutory formula and may be subject to an additional discount if certain pricing increases more than inflation. State Medicaid

programs and Medicaid managed care plans can seek additional " supplemental " rebates from manufacturers in connection with states' establishment of preferred drug lists. A further requirement for Medicaid coverage is that manufacturers of single source and innovator multiple source drugs enter into a Master agreement and Federal Supply Schedule, or FSS, agreement with the Secretary for Veterans Affairs and charge no more than statutory ceiling prices to the Department of Veteran Affairs, the Department of Defense and certain other federal agencies. Similarly, in order for a covered outpatient drug to receive federal reimbursement under the Medicare Part B and Medicaid programs, the manufacturer must extend discounts on the covered outpatient drug to entities that are enrolled and participating in the 340B drug pricing program, which is a federal program that requires manufacturers to provide discounts to certain statutorily- defined safety- net providers. The 340B discount for each product is calculated based on certain Medicaid Drug Rebate Program metrics that manufacturers are required to report to CMS. Emflaza is also eligible for reimbursement under the Medicare Part D program. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities, which will provide coverage of outpatient prescription drugs. Part D prescription drug formularies are required to include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any negotiated prices for our products covered by a Part D prescription drug plan likely will be lower than the prices we might otherwise obtain, and payment of Medicare Coverage Gap discounts may further reduce realization on Part D drugs. Further, CMS is proposing to relax Part D coverage requirements to give plans more leverage in negotiating their formularies. With respect to drugs eligible for reimbursement under Medicare Part B, on November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nations payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capita Gross Domestic Product- adjusted (GDP- adjusted) price of any non- U. S. member country of the Organisation for Economic Co- operation and Development ~~80~~ (OECD) with a GDP per capita that is at least sixty percent of the U. S. GDP per capita. This rule now has been rescinded but other measures, including the Inflation Reduction Act of 2022, or IRA, have been enacted to address the costs of pharmaceuticals. Such rules and any additional healthcare reform measures could further constrain our business or limit the amounts that federal and state governments will pay for healthcare products and services, which could result in additional pricing pressures. ~~In~~ **77In** addition, U. S. private health insurers often rely upon Medicare coverage policies and payment limitations in setting their own coverage and reimbursement policies. Any such coverage or payment limitations may result in a similar reduction in payments from non- governmental payors. Payment by private payors is also subject to payor- determined coverage and reimbursement policies that vary considerably and are subject to change without notice. We expect that coverage and reimbursement of Emflaza in the United States will vary from commercial payor to commercial payor. Many commercial payors, such as managed care plans, manage access to prescription drugs partly to control costs to their plans, and may use drug formularies and medical policies to limit their exposure. Exclusion from policies can directly reduce product usage in the payor' s patient population and may negatively impact utilization in other payor plans, as well. There has been recent negative publicity and increasing legislative and public scrutiny around pharmaceutical drug pricing in the U. S., in particular with respect to orphan drugs and specifically with respect to Emflaza. Moreover, U. S. government authorities and third- party payors are increasingly attempting to limit or regulate drug prices and reimbursement, often with particular focus on orphan drugs. These dynamics may give rise to heightened attention and potential negative reactions to pricing decisions for Emflaza and products for which we may receive regulatory approval in the future, possibly limiting our ability to generate revenue and attain profitability. Moreover, in 2017, the U. S. Congress modified and amended certain provisions of the 2010 U. S. healthcare reform legislation (the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, known collectively as the Affordable Care Act), which could have an impact on coverage and reimbursement for healthcare items and services covered by the federal and state healthcare programs as well as plans in the private health insurance market. The so- called " individual mandate " was repealed as part of tax reform legislation adopted in December 2017. Legal challenges to the Affordable Care Act continue to arise and there may be future efforts to modify, repeal, or otherwise invalidate all, or certain provisions of the Affordable Care Act. The Biden administration is expected to continue to take measures to further facilitate the implementation of the Affordable Care Act. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results and we cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business. Additionally, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. Failure of the Joint Select Committee on Deficit Reduction to reach required deficit reduction goals triggered the legislation' s automatic reduction to several government programs. This legislation resulted in aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. However, pursuant to the CARES Act and subsequent legislation, these Medicare sequester reductions were suspended through the end of March 2022 and from April 2022 through June 2022, a 1 % cut was in effect, with the full 2 % cut remaining thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidates is prescribed or used. In the EU, reference pricing systems and other measures may lead to cost containment and reduced prices with respect to Translarna for the treatment of nmDMD, Upstaza for the treatment of AADC deficiency and other product candidates that might receive marketing authorization in the future. Our inability to promptly obtain coverage and profitable payment rates from both government- funded and private payors for our product or any of our product candidates that may receive marketing authorization, or a reduction in coverage for payment rates for our product or any such product candidates, could have a material adverse effect on our business, results of operations and financial condition. In addition, in the EU, an authorized trader, such as a wholesaler, can purchase a medicine in one EU member state and obtain a license to import

the product into another EU member state. This process is called " parallel distribution ". As a result, a purchaser in one EU ~~81member~~ -- **member** state may seek to import Translarna from another EU member state where Translarna is sold at a lower price. This could have a negative impact on our business, financial condition, results of operations and growth. Similarly, sales of Emflaza in the United States could also be reduced if deflazacort is imported into the United States from lower- priced markets, whether legally or illegally. For example, in the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Mexico and Canada. In October 2020, the Department of Health and ~~Human~~ **78Human** Services, or HHS, and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. **Certain** ~~The final rule is currently the subject of ongoing litigation, but at least six~~ states ~~(Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire)~~ have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by **the FDA. Florida recently received approval for its SIP from** the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. ~~The implementation of the rules has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation~~ . The rule also creates a safe harbor for price reductions reflected at the point- of- sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and ~~manufactures~~ **manufacturers** ~~, the implementation~~ **. The effective date** of ~~which has been~~ **the new safe harbors and the revision to the discount safe harbor was** delayed **by court order** until January 1, ~~2026~~ **2023** ~~by~~ **. Recent legislation further delayed implementation of** the ~~Infrastructure Investment~~ **new safe harbors** and ~~Jobs Act~~ **the revision to the discount safe harbor until January 1, 2032** . Risks Related to Our Financial Position and Need for Additional CapitalWe have incurred significant losses since our inception and based on our current commercial, research and development plans, we expect to continue to incur significant operating expenses for the foreseeable future. We may never generate profits from operations or maintain profitability. Since inception, we have incurred significant operating losses. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~2~~ **3** , ~~657~~ **283** . ~~0~~ **6** million. We have ~~historically~~ financed our operations **to date** primarily through the **private offerings** ~~issuance and sale~~ of ~~our common stock in~~ **convertible senior notes,** public **and** ~~offerings, our~~ " at the market offerings " of ~~our~~ common stock, ~~our initial public offering,~~ proceeds from ~~the Royalty~~ **royalty** ~~Purchase~~ **purchase** ~~Agreement~~ **agreements** , net proceeds from our borrowings under ~~the~~ **our** ~~Credit~~ **credit** ~~Agreement~~ **agreement with** ~~, or the~~ Blackstone ~~Credit Agreement~~ , ~~dated as of October 27, 2022, among us, as the Borrower, the subsidiaries of the Borrower from time to time party thereto, as Guarantors, the Lenders from time to time party thereto and Wilmington Trust, National Association, as Administrative Agent, the~~ private placements of our **convertible** preferred stock and common stock, collaborations, bank and institutional lender debt, other convertible debt, grant funding and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease ~~areas~~ **area** addressed by our product candidates. We have relied on revenue generated from net sales of Translarna for the treatment of nmDMD in territories outside of the United States since 2014, Emflaza for the treatment of DMD in the United States since 2017, and Upstaza for the treatment of AADC deficiency in the EEA since May 2022. We have also relied on revenue associated with milestone and royalty payments from Roche pursuant to the SMA License Agreement under our SMA program **and** ~~. We also began to recognize~~ revenue generated from net sales of Tegsedi ~~for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in 2019~~ and Waylivra ~~for the treatment of FCS in 2020~~ in Latin America and the Caribbean. Based on our current commercial, research and development plans, we expect to continue to incur significant operating expenses for the foreseeable future, which we anticipate will be partially offset by revenues generated from the sale of our products and our collaboration and royalty revenues. We expect to continue to generate operating losses through ~~2023~~ **2024** and, while we anticipate that operating losses generated in future periods should decline versus prior periods, we may never generate profits from operations or maintain profitability. The net losses we incur may fluctuate significantly from period to period. From time to time, we have engaged in strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets or businesses. In connection with these acquisitions, we have entered into agreements through which we have ongoing obligations, including obligations to make contingent payments upon the achievement of certain development, regulatory and net sales milestones or upon a percentage of net sales of certain products. See " Item 1. Business- Our Ongoing Acquisition- Related Obligations " for further information regarding our acquisitions and our ongoing obligations. We may engage in additional strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations and we may incur expenses, including with respect to transaction costs, subsequent ~~82development~~ -- **development** costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction. Our current ability to generate revenue from sales of Translarna is dependent upon our ability to maintain our marketing authorizations in the EEA for Translarna for the treatment of nmDMD in ambulatory patients aged two years and older, in Russia for the treatment of nmDMD in patients aged two years and older and in Brazil for the treatment of nmDMD in ambulatory patients two years and older and for continued treatment of patients that become non- ambulatory **, as well as in various other countries** . The marketing authorization in the EEA is subject to annual review and renewal by the **EC** ~~European Commission~~ following reassessment by the EMA of the benefit- risk balance of the authorization **. For example** ~~and is further subject to a specific obligation to conduct and report the results of Study 041~~ , **in February 2023** ~~a multi- center~~ , **we submitted** ~~randomized, double- blind, 18- month, placebo- controlled trial, followed by~~ an **annual** ~~18- month open- label extension, according to an agreed protocol, in order to confirm the efficacy and safety of Translarna. Enrolling, conducting and reporting a clinical trial is a time- consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. We may experience unknown complications with Study 041 and may not achieve the pre- specified endpoint with statistical significance, which would have a material adverse~~

~~effect on our ability to maintain our~~ marketing authorization **request to** ~~in the EEA. If, in any annual renewal cycle,~~ the EMA **. In September 2023,** ~~determines that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with the specific obligation to complete Study 041 or any other~~ - - **the CHMP gave a negative opinion** ~~requirement that has been or may be placed~~ on the **conversion of the conditional** marketing authorization **to the full marketing authorization of Translarna for the treatment of nmDMD and a negative opinion on the renewal of the existing conditional marketing authorization of 79Translarna. On January 25** , **2024, the CHMP issued a negative opinion for the renewal of the conditional marketing authorization following a re- examination procedure. In accordance with EMA regulations, the EC has 67 days to adopt the opinion from the date of its issuance. If the EC adopts the negative opinion, Translarna would no longer have marketing authorization in the EEA. For more information regarding the risks associated with the a potential EC adoption of the CHMP' s negative opinion on Translarna' s marketing authorization, see Item 1A. Risk Factors, " We may be unable to continue to commercialize Translarna for nonsense mutation Duchenne muscular dystrophy in the European Economic Area if** the European Commission **adopts** ~~could, at~~ the **negative opinion issued by the Committee** ~~EMA' s recommendation, vary, suspend, withdraw or~~ **for** ~~refuse to~~ **Medicinal Products for Human Use of the European Medicines Agency for the** ~~renew~~ **renewal of** the ~~marketing~~ **existing conditional** authorization for Translarna ~~or impose other specific obligations or restrictions, which would have a materially adverse effect on our business~~ . **"** ~~We expect to incur significant costs in connection with our efforts to maintain our marketing authorization in the EEA. If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or a reimbursed early access program, or EAP program, and throughout all territories.~~ We also expect that our efforts to advance Translarna for the treatment of nmDMD in the United States will be time- consuming and may be expensive. We anticipate that **we** ~~our expenses~~ will continue to ~~increase~~ **incur significant expenses** in connection with our commercialization efforts in the United States, the EEA, Latin America and other territories, including ~~the expansion of~~ **expenses related to** our **commercial** infrastructure and corresponding sales and marketing, legal and regulatory, **and** distribution and manufacturing ~~and~~ **undertakings as well as** administrative and employee- based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with ongoing, planned and potential future clinical trials and studies ~~in~~ **for sepiapterin and** our splicing ~~, gene therapy, Bio- e, metabolic~~ and ~~oncology~~ **ferroptosis and inflammation** programs as well as studies in our products for maintaining authorizations, ~~including Study 041,~~ label extensions and additional indications. We ~~have begun seeking and intend to~~ continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories ~~outside of~~ **that we do not currently have marketing authorization in and we are exploring other potential mechanisms in which we may provide Translarna to nmDMD patients in** the EEA ~~, Brazil and Russia~~ **if the EC adopts the CHMP' s negative opinion for Translarna** . We **anticipate submitting** ~~are also preparing~~ a BLA **to the FDA** for Upstaza for the treatment of AADC deficiency in the United States **in March 2024. We also expect to submit** ~~and~~ - **an MAA to the EMA for sepiapterin for the treatment of PKU in March 2024 and** we ~~anticipate~~ **expect to** ~~submitting~~ ---- **submit** ~~a BLA~~ **an NDA** to the FDA ~~in~~ **for sepiapterin for** the **treatment** ~~first half~~ of **PKU no later than the third quarter of** ~~2023~~ **2024** . These efforts may significantly impact the timing and extent of our commercialization **and manufacturing** expenses. In addition, the clinical and regulatory developments noted in this risk factor may exacerbate the risks related to our commercialization efforts set forth under the heading " Risks Related to the Development and Commercialization of our Products and our Product Candidates, " which could increase the costs associated with our commercial activities or have a negative impact on our revenues. We may seek to continue to expand and diversify our product pipeline through opportunistically in- licensing or acquiring the rights to products, product candidates or technologies and we may incur expenses, including with respect to transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction, which would increase our future capital requirements. With respect to our outstanding 1. 50 % convertible senior notes due September 15, 2026, or the 2026 Convertible Notes, cash interest payments are payable on a semi- annual basis in arrears, which will require total funding of $ 4. 3 million annually. ~~With~~ **We** ~~respect~~ - **expect** to **pay** ~~borrowings under~~ the **former equityholders** ~~Blackstone Credit Agreement, cash interest payments are payable on the applicable interest payment dates for each loan thereunder. In addition, we will be required under conditions specified in the Blackstone Credit Agreement to fund a reserve account up to certain amounts specified therein. The funds in the reserve 83account are available to prepay the Loans at any time at our option, and are, if funded, subject to release upon certain further conditions. Upon any such release, such funds are freely available for use by us subject to the generally applicable terms and conditions~~ of **Agilis** ~~the Blackstone Credit Agreement. Furthermore, the Blackstone Credit Agreement covenant requiring us to have consolidated liquidity of at least~~ $ ~~100~~ **20** . 0 million ~~as of~~ **in development milestone payments upon** the ~~last day~~ **acceptance for filing by the FDA** of ~~each fiscal quarter will be increased to~~ **a BLA for Upstaza for the treatment of AADC deficiency and** $ ~~200~~ **4. 5 million in regulatory milestones for the approval of the BLA from the FDA pursuant to the Agilis Merger Agreement. We anticipate submitting a BLA to the FDA for Upstaza for the treatment of AADC deficiency in the United States in March 2024. We also expect to make payments to the former Censa securityholders of $ 65** . 0 million ~~if we consummate acquisitions meeting certain consideration thresholds described~~ in the ~~Blackstone Credit Agreement. In February~~ **aggregate in cash upon the potential achievement in** ~~2023~~ **2024** ~~, we completed enrollment~~ of **regulatory milestones relating to** ~~our Phase 3 placebo- controlled clinical trial for~~ sepiapterin **pursuant to** ~~for PKU. In connection with this event and in accordance with the Agreement and Plan of Merger, dated as of May 5, 2020, or~~ the Censa Merger Agreement ~~, by and among us, Hydro Merger Sub, Inc., our wholly owned, indirect subsidiary, and, solely in its capacity as the representative, agent and attorney- in- fact of the securityholders of Censa Pharmaceuticals, Inc., or Censa, Shareholder Representative Services LLC, we are obligated to pay a $ 30. 0 million development milestone to the former Censa securityholders, which we have the option to pay in cash or shares of our common stock. We also expect to make additional~~

~~payments to the former Censa securityholders of $ 50. 0 million in the aggregate upon the potential achievement in 2023 of certain development and regulatory milestones relating to sepiapterin. Furthermore, we expect to pay the former equityholders of Agilis an additional $ 20. 0 million upon the acceptance for filing by the FDA of a BLA for Upstaza for the treatment of AADC deficiency, which we expect to occur in the first half of 2023~~ . In addition, our expenses will increase if and as we: ● seek to satisfy contractual and regulatory obligations that we assumed through our acquisitions and collaborations; ● execute our ~~commercial~~ **commercialization** strategy for our products, including initial commercialization launches of our products, label extensions or entering new markets; **80** ● are required to complete any additional clinical trials, non- clinical studies or **Chemistry, Manufacturing and Controls, or** CMC **,** assessments or analyses in order to advance Translarna for the treatment of nmDMD in the United States or elsewhere; ● are required to take other steps ~~, in addition to Study 041,~~ to maintain our current marketing authorization in the EEA, Brazil and Russia for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications; ● ~~utilize the Hopewell Facility to manufacture program materials for certain of our gene therapy product candidates as well as program materials for third parties; ●~~ initiate or continue the research and development of **sepiapterin and** our splicing ~~, gene therapy, Bio- e, metabolic~~ and ~~oncology~~ **ferroptosis and inflammation** programs as well as studies in our products for maintaining authorizations, ~~including Study 041,~~ label extensions and additional indications **; ● continue to utilize the Hopewell Facility to manufacture program materials for third parties** ; ● seek to discover and develop additional product candidates; ● seek to expand and diversify our product pipeline through strategic transactions; ● maintain, expand and protect our intellectual property portfolio; and ● add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts. Our expenses may also increase as a result of economic conditions, such as potentially high inflation rates within the jurisdictions that we operate **, sustained high interest rates,** or unfavorable fluctuations in foreign currency exchange rates. Our ability to generate profits from operations and become and remain profitable depends on our ability to successfully develop and commercialize drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including: ● commercializing and marketing all of our products and products candidates; ● negotiating, securing, and maintaining adequate pricing, coverage and reimbursement terms, on a timely basis, with third- party payors for our products and product candidates; ● maintaining ~~the~~ **our** marketing authorization ~~of~~ **for** Translarna for the treatment of nmDMD in the EEA **following** ~~, including successfully obtaining annual renewals of~~ the ~~marketing authorization, fulfilling~~ **CHMP' s negative opinion on** the **conditional** ~~specific obligation to conduct 84and report the results of Study 041 to the EMA, and meeting any ongoing requirements related to the~~ marketing authorization; ● advancing Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non- clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA re- submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States ~~;~~ ~~● maintaining orphan exclusivity in the United States for Emflaza~~ ; ● successfully completing any post- marketing requirements imposed by regulatory agencies with respect to our products; ● expanding the territories in which we are approved to market our products; ● successfully advancing our other programs and collaborations, including **sepiapterin and** our splicing ~~, gene therapy, Bio- e, metabolic~~ and ~~oncology~~ **ferroptosis and inflammation** programs as well as studies in our products for additional indications; ● maintaining a global commercial infrastructure, including the sales, marketing and distribution capabilities to effectively market and sell our products and product candidates throughout the world; ● implementing marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization; ● identifying patients eligible for treatment with our products and product candidates; ● successfully developing or commercializing any product candidate or product that we may in- license or acquire; ● protecting our rights to our intellectual property portfolio related to Translarna and other products and product candidates; and ● contracting for the manufacture and distribution of commercial quantities of our products and product candidates. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to generate profits from operations. Even if we do generate profits from operations, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to generate profits from operations and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment in our company. ~~We~~ **81We** may need additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts. As noted in the prior risk factor, we expect to incur significant expenses related to our clinical, regulatory, commercial, legal, research and development, and other business efforts. We believe that our cash flows from product sales, together with existing cash and cash equivalents, **and marketable securities** will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including: ● our ability to **maintain our marketing authorization for Translarna for the treatment of nmDMD in the EEA following the CHMP' s negative opinion on the conditional marketing authorization following a re- examination procedure or identify other potential mechanisms in which we may provide Translarna to nmDMD patients in the EEA; ● our ability to maintain the marketing authorization for Translarna and our other products in territories outside of the EEA; ● our ability to** commercialize and market our products and product candidates **that may receive marketing authorization** ; ● our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms, on a timely basis, with third- party payors for our products and ~~product~~ **products** candidates; ● **the amount of generic drug competition that we face for Emflaza following its loss of orphan drug exclusivity related to the treatment of DMD in patients five years and older; ●** our ability to **obtain** ~~maintain the~~ marketing authorization ~~in~~ **for sepiapterin for** the **treatment of PKU in the United States and** EEA ~~for~~

~~Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit- risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label; ● the timing and outcome of Study 041~~ ; ● our ability to obtain marketing authorization for Upstaza for the treatment of AADC deficiency in the United States; ● the costs, timing and outcome of our efforts to advance Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non- clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA re- submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States; ~~85~~ ● **unexpected decreases in revenue** ~~our~~ **or increase** ~~ability to maintain orphan exclusivity~~ in ~~the United States for Emflaza~~ **expenses resulting from potential widespread outbreaks of contagious disease, such as COVID- 19** ; ● our ability to successfully complete ~~any~~ **all** post-marketing requirements imposed by regulatory agencies with respect to our products; ● the progress ~~,~~ **and** results ~~and costs~~ of ~~our~~ activities ~~under~~ **for sepiapterin and** our splicing ~~, gene therapy, Bio- e, metabolic~~ and ~~oncology~~ **ferroptosis and inflammation** programs as well as studies in our products for maintaining authorizations, label extensions and additional indications; ● the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for **any of** our products and for any of our other product candidates that may receive marketing authorization or any additional ~~indications or~~ territories in which we receive authorization to market **Translarna** ~~our products~~ ; ● ~~our ability to utilize~~ the ~~Hopewell Facility to manufacture~~ **costs, timing and outcome of regulatory review of sepiapterin and our splicing and ferroptosis and inflammation** ~~program~~ **programs and Translarna and Upstaza in other territories** ~~materials for certain of our gene therapy product candidates as well as program materials for third parties~~ ; ● ~~the costs, timing and outcome of regulatory review of our other product candidates, including those in our splicing, gene therapy, Bio- e, metabolic and oncology programs as well as studies in our products for maintaining authorizations, label extensions and additional indications; ●~~ our ability to satisfy our obligations under the ~~Blackstone Credit Agreement; ● our ability to satisfy our obligations under the~~ indenture governing ~~our~~ **the** 2026 Convertible Notes; ● the timing and scope of **any potential future** growth in our employee base **; ● the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our other product candidates, including those in our splicing and ferroptosis and inflammation programs** ; ● revenue received from commercial sales of ~~or~~ **our** products or any of our ~~other~~ product candidates; ● our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for ~~our products and product candidates~~ **Translarna for the treatment of nmDMD** on adequate terms, or at all; ● the ability and willingness of patients and healthcare professionals to access **Translarna** ~~our products and product candidates~~ through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome; **● our ability to continue to utilize the Hopewell Facility to manufacture program materials for third parties; 82** ● the costs of preparing, filing and prosecuting patent applications, maintaining, and protecting our intellectual property rights and defending against intellectual property-related claims; ● the extent to which we acquire or invest in other businesses, products, product candidates, and technologies, including the success of any acquisition, in- licensing or other strategic transaction we may pursue, and the costs of subsequent development requirements and commercialization efforts, including with respect to our acquisitions of Emflaza, Agilis, **our ferroptosis and inflammation platform and** Censa ~~and of BioElectron' s assets,~~ and our licensing of Tegsedi and Waylivra; and ● our ability to establish and maintain collaborations, including our collaborations with Roche and the SMA Foundation, and our ability to obtain research funding and achieve milestones under these agreements. Conducting preclinical testing and clinical trials is a time- consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales for certain product candidates or indications. In addition, our products and product candidates, if approved, may not achieve sustained commercial success. Likewise, if we fail to maintain our marketing authorization or lose non- patent market exclusivity for our products and product candidates, we will be unable to commercialize and generate revenue from the sales of those products. Accordingly, we may need to continue to rely on additional financing in connection with our continuing operations and to achieve our business objectives. In addition, we may seek additional capital due to favorable market conditions or based on strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. Additional financing may not be available to us on acceptable terms or at all. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts ~~. Our indebtedness under the Blackstone Credit Agreement could adversely affect our financial condition or restrict future operations. On October 27, 2022, or the Closing Date, we entered into the Blackstone Credit Agreement for fundings of up to $ 950. 0 million consisting of a committed loan facility of $ 450. 0 million and further contemplating the potential for up to $ 500. 0 86million of additional financing, to the extent that we request such additional financing and subject to the lenders' agreement to provide such additional financing and to mutual agreement on terms. The Blackstone Credit Agreement provides for a senior secured term loan facility funded on the Closing Date in the aggregate principal amount of $ 300. 0 million, or the Initial Loans, and a committed delayed draw term loan facility of up to $ 150. 0 million, or the Delayed Draw Loans and, together with the Initial Loans, the Loans, to be funded at our request within 18 months of the Closing Date subject to specified conditions. In addition, the Blackstone Credit Agreement contemplates the potential for further financings by Blackstone, by providing for incremental discretionary uncommitted further financings of up to $ 500. 0 million. The Loans mature on the date that is seven years from the Closing Date. Borrowings under the Blackstone Credit Agreement bear interest at a variable rate equal to, at our option, either an adjusted Term SOFR rate plus seven and a quarter percent (7. 25 %) or the Base Rate plus six and a quarter percent (6. 25 %), subject to a floor of one percent (1 %) and two percent (2 %) with respect to Term SOFR rate and Base Rate (each as defined in the Blackstone Credit Agreement), respectively. All obligations under the Blackstone Credit Agreement are secured by security interests in certain of our assets, including (1) intellectual property and other assets related to Translarna, Emflaza, Upstaza, sepiapterin and, until certain release conditions are met, vatiquinone, in each case, together with any other forms,~~

~~formulations, or methods of delivery of any such products, and regardless of trade or brand name, (2) future acquired intellectual property (but not internally developed intellectual property unrelated to other intellectual property collateral) and other related assets, and (3) the equity interests held by us in certain of our subsidiaries. The Blackstone Credit Agreement contains certain negative covenants with which we must remain in compliance. The Blackstone Credit Agreement also requires that we maintain consolidated liquidity of at least $ 100. 0 million as of the last day of each fiscal quarter, which shall be increased to $ 200. 0 million upon our consummating acquisitions meeting certain consideration thresholds described therein. In addition, we will be required under conditions specified in the Blackstone Credit Agreement to fund a reserve account up to certain amounts specified therein. The funds in the reserve account are available to prepay the Loans at any time at our option, and are, if funded, subject to release upon certain further conditions. Upon any such release, such funds are freely available for use by us subject to the generally applicable terms and conditions of the Blackstone Credit Agreement. The Blackstone Credit Agreement contains certain customary representations and warranties, affirmative covenants and provisions relating to events of default. In the event of an acceleration of amounts due under the Blackstone Credit Agreement as a result of an event of default, we may not have sufficient funds or may be unable to arrange for additional financing to repay the Loans or to make any accelerated payments, and the lenders could seek to enforce security interests in the collateral securing the Loans, which would have a material adverse effect on our business, financial condition and results of operations. In addition, our indebtedness under the Blackstone Credit Agreement could have significant adverse consequences, including, among other things: ● requiring us to dedicate a substantial portion of cash and cash equivalents and marketable securities to the payment of interest on, and principal of, the Loans, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes; ● obligating us to negative covenants restricting our activities, including limitations on dispositions, mergers or acquisitions, encumbering our intellectual property, incurring indebtedness or liens, paying dividends, making investments and engaging in certain other business transactions; ● limiting our flexibility in planning for, or reacting to, changes in our business and our industry; ● placing us at a competitive disadvantage compared to our competitors who have less debt or competitors with comparable debt at more favorable interest rates; and87 ● limiting our ability to borrow additional amounts for working capital, capital expenditures, research and development efforts, acquisitions, debt service requirements, execution of our business strategy and other purposes. Any of these factors could materially and adversely affect our business, financial condition and results of operations. We intend to satisfy our current and future debt obligations with our existing cash, cash equivalents and available for sale securities, potential future product revenue and funds from external sources. However, our inability to satisfy such obligations for any reason would have a material adverse effect on our business, financial condition and results of operations~~. We may engage in strategic transactions to acquire assets, businesses, or rights to products, product candidates or technologies or form collaborations or make investments in other companies or technologies that could harm our operating results, dilute our stockholders' ownership, increase our debt, or cause us to incur significant expense. As part of our business strategy, we may engage in additional strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations, similar to our acquisitions of Emflaza, Agilis, Censa and BioElectron' s assets and the Tegsedi- Waylivra Agreement. We may not identify suitable strategic transactions, or complete such transactions in a timely manner, on a cost- effective basis, or at all. Moreover, we may devote resources to potential opportunities that are never completed, or we may incorrectly judge the value or worth of such opportunities. Even if we successfully execute a strategic transaction, we may not be able to realize the anticipated benefits of such transaction, may incur additional debt or assume unknown or contingent liabilities in connection therewith, and may experience losses related to our investments in such transactions. Integration of an acquired company or assets into our existing business may not be successful and may disrupt ongoing operations, require the hiring of additional personnel and the implementation of additional internal systems and infrastructure, and require management resources that would otherwise focus on developing our existing business. Even if we are able to achieve the long- term benefits of a strategic transaction, our expenses and short- term costs may increase materially and adversely affect our liquidity. Any of the foregoing could have a detrimental effect on our business, results of operations and financial condition. In addition, future strategic transactions may entail numerous operational, financial and legal risks, including: ● incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions; ● exposure to known and unknown liabilities, including possible intellectual property infringement claims, violations of laws, tax liabilities and commercial disputes; ● higher than expected acquisition and integration costs; ● difficulty in integrating operations and personnel of any acquired business; ● increased amortization expenses or, in the event that we write- down the value of acquired assets, impairment losses; **83** ● impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership; ● inability to retain personnel, customers, distributors, vendors and other business partners integral to an in- licensed or acquired product, product candidate or technology; ● potential failure of the due diligence processes to identify significant problems, liabilities or other shortcomings or challenges; ● entry into indications or markets in which we have no or limited direct prior development or commercial experience and where competitors in such markets have stronger market positions; and ● other challenges associated with managing an increasingly diversified business. If we are unable to successfully manage any strategic transaction in which we may engage, our ability to develop new products and continue to expand and diversify our product pipeline may be limited. ~~88Raising~~ -- **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 enough product revenues to cover our expenses, we expect to supplement our cash needs through a combination of equity offerings, debt financings, **royalty sales,** collaborations, strategic alliances, grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates; marketing, distribution, licensing or other arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our

~~shareholders~~ **stockholders** ' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. **Any** ~~Our senior secured term loan facility with Blackstone as well as any additional~~ debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, entering into agreements involving licenses to our intellectual property, making capital expenditures or declaring dividends. If 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, 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. Our ability to use our net operating losses and certain other tax attributes to offset potential taxable income and related income taxes that would otherwise be due is subject to limitation under the provisions of Sections 382 and 383 of the Internal Revenue Code as a result of ownership changes of the Company and could be subject to further annual limitations under such provisions. In addition, we may not generate sufficient future taxable income to use our net operating losses and certain other tax attributes. If a corporation undergoes an " ownership change " within the meaning of Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or Sections 382 and 383, the corporation' s ability to utilize any net operating losses, or NOLs, and certain tax credits and other tax attributes generated before such an ownership change, is limited. We believe that we have in the past experienced ownership changes within the meaning of Sections 382 and 383 that have resulted in limitations under Sections 382 and 383 (and similar state provisions) on the use of our NOLs and other tax attributes. Sections 382 and 383 are extremely complex provisions with respect to which there are many uncertainties, and we have not requested a ruling from the United States Internal Revenue Service, or IRS, to confirm our analysis of the ownership change limitations related to the NOLs and other tax attributes generated by us. Therefore, we have not established whether the IRS would agree with our analysis regarding the application of Sections 382 and 383. We continue to fully evaluate the impact of a limitation on the use of our NOLs and other tax attributes under Sections 382 and 383. ~~Moreover~~ **84Moreover** , our ability to use these NOLs to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income. We generated taxable income that is subject to income tax in ~~2022~~ **2023** , but continue to maintain NOLs from previous years that will be carried forward. Changes in our effective income tax rates and future changes to U. S. and non- U. S. tax laws could adversely affect our results of operations. We are subject to income taxes in the Unites States and various ex- U. S. jurisdictions. Taxes will be incurred as income is earned in these different jurisdictions. Various factors may have favorable or unfavorable effects on our effective income tax rate. These factors include, but are not limited to, interpretations of existing tax laws, changes in tax laws and rates, the accounting for stock options and other share- based compensation, changes in accounting standards, future levels of research and development spending, changes in the mix and level of pre- tax earnings by taxing jurisdiction, the outcome of examinations by the IRS and other jurisdictions, the accuracy of our estimates for unrecognized tax benefits, the realization of deferred tax assets, or by changes to our ownership or capital structure. The impact on our income tax ~~89provision~~ -- **provision** resulting from the above- mentioned factors and others may be significant and could adversely affect our results of operations. Changes in tax laws or regulations, including further regulatory developments arising from U. S. tax reform legislation as well as multi- jurisdictional changes enacted in response to the action items provided by the Organization for Economic Cooperation and Development (OECD), may increase tax uncertainty and the amount of tax we pay. On December 22, 2017, the United States government enacted the 2017 Tax Act, which significantly reformed the U. S. Internal Revenue Code of 1986, as amended, or the Code. The Tax Act, among other things, contained significant changes to corporate taxation. As part of Congress' s response to the COVID- 19 pandemic, economic relief **legislation** was enacted in 2020 and 2021. Such legislation contains numerous tax provisions. In addition, the IRA was signed into law in August 2022. The IRA introduced new tax provisions, including a 1 % excise tax imposed on certain stock repurchases by publicly traded corporations. The 1 % excise tax generally applies to any acquisition by the publicly traded corporation (or certain of its affiliates) of stock of the publicly traded corporation in exchange for money or other property (other than stock of the corporation itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases. Regulatory guidance under the 2017 Tax Act, the IRA, and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. In addition, it is uncertain if and to what extent various states will ~~confirm~~ **conform** the **2017** ~~IRA, the~~ Tax Act **, IRA** , and additional tax legislation ~~. Regulatory guidance under the 2017 Tax Act, which was enacted on December 22, 2017, the FFCR Act, the CARES Act, the CAA, and the ARPA is and continues to be forthcoming, and such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. It is also possible that Congress will enact additional legislation in connection with the COVID- 19 pandemic, and as a result of the changes in the U. S. presidential administration and control of the U. S. Senate, additional tax legislation may also be enacted~~ . Although we monitor actual and potential changes to the tax laws in the United States and other jurisdictions, it is very difficult to assess to what extent these changes may impact the way in which we conduct our business or our effective tax rate due to the unpredictability and interdependency of these changes. Changes in tax laws and related regulations and practices could have a material adverse effect on our business operations, cash flows, effective tax rate, financial position and results of operations. Risks Related to Regulatory Approval of our Products and our Product ~~CandidatesOur~~ **CandidatesWe** ~~marketing authorization in the EEA for Translarna for the treatment of nmDMD is a " conditional marketing authorization " that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit- risk balance of the authorization, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of such marketing authorization in any future renewal cycle, we could lose all, or a significant portion of, our ability to generate revenue from sales~~

~~of Translarna, whether pursuant to a commercial or an EAP program, which would have a material adverse effect on our business, financial performance and results of operations. Our marketing authorization in the EEA for Translarna for the treatment of nmDMD is a " conditional marketing authorization " that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit- risk balance of the authorization and is further conditioned upon the conduct of Study 041. We received initial marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older from the European Commission in August 2014 as a " conditional marketing authorization. " In July 2018, the European Commission approved a label- extension request to our marketing authorization for Translarna in the EEA to include patients from two to up to five years of age. In July 2020, the European Commission approved the removal of the statement " efficacy has not been demonstrated in non- ambulatory patients " from the indication statement for Translarna. The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit- risk balance of the authorization In June 2022, we announced top- line results from the placebo- controlled trial of Study 041. Within the placebo- controlled trial, Translarna showed a statistically significant treatment 90benefit across the entire intent to treat population as assessed by the 6- minute walk test, assessing ambulation and endurance, and in lower- limb muscle function as assessed by the North Star Ambulatory Assessment, a functional scale designed for boys affected by DMD. Additionally, Translarna showed a statistically significant treatment benefit across the intent to treat population within the 10- meter run / walk and 4- stair stair climb, each assessing ambulation and burst activity, while also showing a positive trend in the 4- stair stair descend although not statistically significant. Within the primary analysis group, Translarna demonstrated a positive trend across all endpoints, however, statistical significance was not achieved. Translarna was also well tolerated. In September 2022, we submitted a Type II variation to the EMA to support conversion of the conditional marketing authorization for Translarna to a standard marketing authorization, which included a report on the placebo- controlled trial of Study 041 and data from the open- label extension. We expect an opinion from the Committee for Medicinal Products for Human Use in the first half of 2023. Given that statistical significance was not achieved in the placebo- controlled portion of Study 041 within the primary analysis group, the EMA may deny our request for conversion and our annual reassessment by the EMA of the benefit- risk balance of the authorization may be negatively impacted as well. We may also still experience unknown complications with open- label extension period Study 041, which would have a materially adverse effect on our ability to maintain our marketing authorization in the EEA. We are further required to implement measures, including pharmacovigilance plans, which are detailed in the risk management plan. If we fail to satisfy our obligations under the marketing authorization, or if it is determined in any annual renewal cycle that the balance of benefits and risks of using Translarna has changed materially, the European Commission could, at the EMA' s recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna. The EMA may also impose other new conditions to our marketing authorization (in addition to Study 041), and may make other recommendations, including new label restrictions. In the event that we do secure annual renewal of the marketing authorization for any given annual renewal cycle, the EMA could nevertheless later determine that we have not complied, or are unable to comply, with any conditions that have been or may be placed on the marketing authorization, including those related to Study 041, which could result in the withdrawal of our marketing authorization or other outcome that would have a materially adverse effect on our business, results of operations and financial condition. If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business, results of operations and financial condition. We~~ may not be able to obtain orphan drug exclusivity for our products or product candidates in either the United States or the EU. Regulatory authorities in some jurisdictions, including the EU and the United States, may designate drugs for relatively small patient populations as orphan drugs. We have obtained orphan drug designations from the EMA and from the FDA for Translarna for the treatment of nmDMD, Upstaza for the treatment of AADC, Evrysdi for the treatment of SMA, ~~PTC- AS for the treatment of Angelman syndrome,~~ sepiapterin for the treatment of patients with hyperphenylalaninemia, including hyperphenylalaninemia caused by PKU, vatiquinone for the treatment of Friedreich ataxia ~~,~~ **and** utreloxastat for the treatment of ALS ~~and unesbulin for the treatment of LMS~~ . The FDA has also granted an orphan drug designation to Emflaza for the treatment of DMD ~~, vatiquinone for the treatment of seizures in patients with mitochondrial disease, unesbulin for the treatment of DIPG and PTC- FA for the treatment of Friedreich ataxia~~ . We may also seek orphan drug **designation and** exclusivity for other product candidates, if we believe that the product candidate may qualify. We, however, may not be able to obtain ~~orphan~~ **85orphan** drug designation in the future for any of our other product candidates. Obtaining orphan drug exclusivity, both in the EU and in the United States, may be important to a product candidate' s future success. In the EU, if an orphan designated product subsequently receives the first marketing authorization for the indication for which it has received such a designation, the product is entitled to 10 years of market exclusivity, which, subject to certain exceptions, precludes the EMA from accepting another marketing application for a similar medicinal product, even if the new marketing application relies on independently generated data submitted as part of a full marketing authorization application dossier. The EU exclusivity period can be reduced to six years, at the end of the fifth year, if a drug no longer meets the criteria for orphan drug designation, including if the drug is sufficiently profitable so that market exclusivity is ~~91no~~ **no** longer justified. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to the orphan product. In this context, a " similar medicinal product " is a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. Product candidates can also lose orphan designation, and the related benefits, prior to obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met **. The EC has conducted a review of the Orphan Drug Regulation together with the Paediatric Regulation. The outcome of this review**

is intended to guide future legislative changes and shape the EU' s pharmaceutical strategy . In the United States, under FDA' s current policy, if a product with an orphan drug designation subsequently receives the first marketing authorization for the indication for which it has such designation, the product is entitled to seven years of market exclusivity which precludes the FDA from approving another marketing application for the " same drug " for the same orphan designated approved indication for that time period. When determining whether a drug is the " same drug " as an orphan designated product, the FDA looks to the products' molecular features and use. The specific sameness criteria, however, varies based on whether the product is composed of small or large molecules and if the product is a gene therapy. Moreover, for gene therapies, the sameness criteria is currently evolving. For example, the FDA ~~recently~~ issued a final guidance document specific to sameness determinations. Depending on product characteristics, sameness may be determined by the FDA on a case by case basis, making it difficult to predict when FDA may approve a product and whether periods of exclusivity will effectively block competitors seeking to market products that are the same or similar to ours for the same intended use. Moreover, following the Catalyst Pharms., Inc. v. Becerra and FDA' s subsequent statement that it intends to continue to apply its regulations tying the scope of orphan- drug exclusivity to the uses or indications for which a drug is approved, as further described in this filing, the exact scope of orphan drug exclusivity may be an evolving space. Accordingly, whether any of our products or product candidates will be deemed to be the same as another product or product candidate is uncertain and the scope of any potential or received orphan drug exclusivity period may be subject to revision. Obtaining orphan drug designation does not guarantee that we will be able to receive ultimate marketing approval. Orphan drug designation neither shortens the development time or regulatory review time of a product candidate nor gives the product candidate any advantage in the regulatory review or approval process. Moreover, the FDA may grant orphan drug designation to multiple products that are considered to be the " same drug " for the same indication. If a competitor obtains an orphan drug designation for and approval of a product with orphan drug exclusivity for the same indication as one of our product candidates before we do and if the competitor' s product is the same drug, in the United States or a similar medicinal product, in the EU, as ours, we could be excluded from the market for a period of time. We also may not be able to maintain any orphan drug designations or exclusivities. For instance, orphan drug designations may be revoked if the FDA finds that the request for designation contained an untrue statement of material fact or omitted material information, or if the FDA finds that the product candidate was not eligible for designation at the time of the submission of the request. Even if we are able to receive and maintain orphan drug designations, we may ultimately not receive any period of regulatory exclusivity if our product candidates are approved. For instance, we may not receive orphan product regulatory exclusivity if the indication for which we receive FDA approval is broader than the orphan drug designation. Orphan exclusivity may also be lost for the same reasons that designation may be lost. Orphan exclusivity may further be lost if we are unable to assure a sufficient quantity of the product to meet the needs of patients with the rare disease or condition. ~~Further~~ **86Further** , even if we do receive orphan drug exclusivity upon approval of a product candidate, this exclusivity is not absolute. For example, if a competitive product that is the same drug or a similar medicinal product as one of our approved products with orphan exclusivity is shown to be " clinically superior " to our product candidate as determined by the FDA or EMA, respectively, any orphan drug exclusivity we have obtained will not block the approval of such competitive product. Orphan exclusivity also would not block FDA from approving a drug that is the same as our product candidates for different indications or products that are different from ours for the same indication. Moreover, marketing exclusivity would not prevent a provider from prescribing or using another drug off- label and third- party payors may reimburse for products off- label even if not indicated for the orphan condition. For certain of our products, periods of orphan drug exclusivity are important. For instance, for Emflaza, we ~~rely~~ **have previously relied** on non- patent market exclusivity periods under the Orphan Drug Act to commercialize Emflaza in the United States. Emflaza' s seven- year period of orphan drug exclusivity related to the treatment of DMD in patients five years and older ~~expires~~ **expired** in ~~92February~~ -- **February** 2024 ~~while its~~ **. We expect the expiration of this orphan drug exclusivity to have significant negative impact on Emflaza net product revenue. Emflaza' s** orphan drug exclusivity related to the treatment of DMD in patients two years of age to less than five expires in June 2026. ~~If~~ **With the expiration of the orphan exclusivity for the Emflaza indication of the treatment of DMD in patients five years and older,** we ~~are~~ **expect to face competition from generic versions of Emflaza for this indication and will likely be priced less than Emflaza. Healthcare providers may also substitute the generic version (s) of Emflaza for patients two years of age to five, despite the fact that the generic version (s) will** not ~~able to maintain orphan drug exclusivity for Emflaza or if another company is able to overcome this exclusivity, we may~~ be ~~materially harmed~~ **approved for such indication until after June 2026** . The respective orphan designation and exclusivity frameworks in the United States and in the EU are subject to change, and any such changes may affect our ability to obtain, or the impact of obtaining, EU or United States orphan designations in the future. All pharmaceutical products for which marketing authorization has been granted are subject to extensive and rigorous governmental regulation and could be subject to restrictions or withdrawal from the market. We may also be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved, as well as our product candidates during development. We, our products and product candidates, our operations, our facilities, our suppliers and our contract manufacturers, distributors, contract research organizations, clinical trial sites and contract testing laboratories are subject to extensive regulation by governmental authorities in the EEA, the United States, and other territories, with regulations differing from country to country. We are not permitted to market our product candidates in the EEA, the United States, or other territories until we have received requisite regulatory approvals. In order to receive and maintain such approvals, and to be compliant with regulatory authority requirements, we and our third- party service providers must comply on a continuous basis with a broad array of regulations and requirements. Depending on the stage of product development and whether a product is approved these requirements may relate to establishment registration and product listing, the payment of user fees, manufacturing processes, risk management measures, quality and pharmacovigilance systems (including reporting of manufacturing deviations and adverse events), pre- and post- approval clinical and pre- clinical data,

labeling, packaging, advertising, marketing and promotional activities (including product sampling), record keeping, distribution, storage, and import and export of pharmaceutical products. Any regulatory approval of any of our products or product candidates, once obtained, may be withdrawn. For example, our marketing authorization for Translarna for the treatment of nmDMD in the EEA is subject to annual review and renewal by the **EC** ~~European Commission~~ following reassessment by the EMA of the benefit- risk balance of the authorization, as well as the specific obligation to conduct and report the results of Study 041 **. On January 25, 2024, the CHMP issued a negative opinion for the renewal of the conditional marketing authorization. In accordance with EMA regulations, the EC has 67 days to adopt the opinion from the date of its issuance. If the EC adopts the negative opinion, Translarna would no longer have marketing authorization in the EEA** . After approving a drug, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. Requirements for additional clinical trials and studies to confirm safety and effectiveness may be imposed as a condition of marketing approval. In addition, the FDA requires surveillance programs to monitor approved products that have been commercialized, as well as REMS, and the agency has ~~the~~ **87the** power to require changes in labeling or to prevent further marketing and distribution of a product. For example, we were obligated to perform certain FDA post- marketing requirements in connection with our marketing authorization for Emflaza in the United States, including pre- clinical and clinical safety studies. Additionally, our marketing authorizations for Translarna, Tegsedi and Waylivra in Brazil and our marketing authorization for Translarna in Russia are subject to renewal every five years. There is no guarantee that we will be able to complete our post- marketing obligations in accordance with the established timetables. Failure to complete the required studies in accordance with the established timetables or failure to provide the requisite periodic reports on the status of post- marketing studies in the absence of good cause could result in an enforcement action. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing and distribution. Regulatory authorities conduct ongoing reviews and inspections or remote regulatory assessments of marketed products, as well as sponsors and manufacturing facilities. Regulatory authorities also conduct inspections of manufacturing facilities and clinical trial sites before approving a product, which can delay approval. If compliance issues are found, it could also result in refusal to approve marketing applications, disruption of production or distribution of a product or product candidate, disruption, cancellation, or suspension of a study, or require substantial resources to correct. Even if marketing authorization of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed, the product may have labeling that includes significant restrictions, warnings, including black box warnings, and contraindications, the regulatory authorities may not approve label claims ~~93neccessary~~ -- **necessary** for successful product marketing, or the approval may be subject to significant conditions of approval, including the requirement of a REMS. A regulatory authority also may impose requirements for costly post- marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. In addition, the competent authorities of each EU member state and the FDA closely regulate the post- approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling and regulatory requirements. Such regulatory authorities can and do impose stringent restrictions on our communications regarding off- label use and if we do not comply with the laws governing promotion of approved drugs, we may be subject to enforcement action for off- label promotion. For example, violations of the FDCA relating to the promotion of prescription drugs may lead to civil and criminal penalties, investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws. In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, both before and after product approval, may yield various results which could negatively affect our business, including: ● restrictions on such products, manufacturers or manufacturing processes; ● changes to or restrictions on the labeling or marketing of a product; ● modifications to promotional pieces; ● issuance of corrective information; ● clinical holds or termination of clinical trials; ● changes in the way a product is administered; ● liability for harm caused to patients or subjects; ● adverse publicity, reputational harm, or the product becoming less competitive; ● regulatory authority issuance of safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the product; ● restrictions on product distribution or use; ● requirements to implement a REMS; ● requirements to conduct post- marketing studies or clinical trials; ● warning, cyber or untitled letters; ● withdrawal of the products from the market or marketing suspensions; ● refusal to approve pending applications or supplements to approved applications that we submit; ● recall of products; ● fines, restitution or disgorgement of profits or revenues; ● suspension or withdrawal of marketing authorizations; **88** ● refusal to permit the import or export of our products; ● product seizure or detention; ● injunctions; ● the imposition of civil or criminal penalties; or ● FDA debarment, suspension and debarment from government contracts, and refusal of orders under existing government contracts, exclusion from federal healthcare programs, consent decrees, or corporate integrity agreements. Non- compliance with regulatory 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 regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions. Not only will we be responsible for our own conduct, but we will also be responsible for the conduct of our employees, independent contractors, consultants, commercial partners, manufacturers, investigators, and contract research organizations. To the extent that any of these third parties engage in intentional, reckless, negligent, or unintentional failures to comply applicable legal and regulatory requirements, we may be subject to regulatory enforcement action, legal actions and liability, and serious harm to our reputation. Moreover, it is possible for a whistleblower to pursue a False ~~94Claims~~ -- **Claims** Act case against us as a result of such third party conduct, even if the government considers the claim unmeritorious and declines to intervene, which could require us to incur costs defending against such a claim. Any of the above events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, or could

substantially increase the costs and expenses of developing and commercializing such product, which in turn could delay or prevent us from generating significant revenues from its sale. Any of these events could further have other material and adverse effects on our operations and business and could adversely impact our stock price and could significantly harm our business, financial condition, results of operations, and prospects. We may face competition from biosimilar, generic, and similar products approved through abbreviated pathways, as well as products approved pursuant to full applications. Our approved products may face competition from products approved via abbreviated pathways as well as products approved pursuant to full applications. For example, our biologic products may face competition from biosimilar or interchangeable products. Sponsors seeking approval of biosimilar or interchangeable products to ours would reference our product in their applications. The applicable laws, however, establish certain protections for reference biologic products. For example, there is a complex and involved framework for sponsors to bring patent infringement actions and actions for declaratory judgment. Accordingly, we may need to pursue costly and time- consuming patent infringement actions, which may include certain statutorily specified regulatory steps before an infringement action may be brought. We may also need to spend time and money defending an action for declaratory judgement that is brought by the biosimilar product sponsor. Another protection established for biologic products is a period of 12 years of exclusivity for reference products that begins on the date that the reference product was first licensed by the FDA. During this time, the FDA may not make the licensure of a biosimilar product effective. Biosimilar applications can, however, be submitted for FDA review beginning four years after the date of the reference product' s first licensure. This exclusivity period, however, is subject to certain limitations. For example, certain changes and supplements to an approved BLA, and certain subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12- year exclusivity period. Moreover, there have been legislative efforts to decrease this period of exclusivity to a shorter timeframe. Future proposed budgets, international trade agreements and other arrangements or proposals may affect periods of exclusivity. Further, even if our biologic product candidates qualify for biologic exclusivity, there is a risk that the FDA will not consider 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, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non- biological products is not yet fully clear, and will depend on a number ~~of 89~~**of** marketplace and regulatory factors that are still developing. It is also possible that payers will give reimbursement preference to biosimilars, even over reference biologics, absent a determination of interchangeability. Similarly, in the EU, another company could gain approval for a competing product based on an MAA with a completely independent data package that includes pharmaceutical tests, preclinical tests and clinical trials. For small molecule drug products, a pharmaceutical manufacturer may file an ~~abbreviated new drug application, or~~ ANDA ~~,~~ seeking approval of a generic copy of one of our approved products. A manufacturer could also submit an NDA under section 505 (b) (2), referencing the FDA' s finding of safety and efficacy for one of our drug products, while also conducting its own studies to support any product changes. Any ANDA or 505 (b) (2) NDA products referencing our approved products would be required to submit patent certifications to the FDA. Unless the applicant does not seek approval until any of our Orange Book listed patents expire or, to the extent possible, carve out any of our Orange Book listed method of use patents, such an applicant would be required to submit what is known as a " Paragraph IV certification, " challenging the validity or enforceability of, or claiming non- infringement of, the listed patent or patents. This would provide us with an opportunity to sue to enforce our patents, which would stay any FDA approval for 30 months from the patent or application owner' s receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent is favorably decided in the applicant' s favor or settled, or such shorter or longer period as may be ordered by a court. While this would delay the approval of the generic or 505 (b) (2) product, such actions would require significant time and cost. ~~95Our~~ -- **Our** small molecule drug products may also be eligible for certain periods of regulatory exclusivity (e. g., five years for new chemical entities, three years for changes to an approved drug requiring a new clinical study, and seven years for orphan drugs), which preclude FDA approval (or in some circumstances, FDA filing and review of) an ANDA or 505 (b) (2) NDA relying on the FDA' s finding of safety and effectiveness for the innovative drug. These exclusivities, however, are also subject to certain limitations. For instance, they would not block FDA acceptance and approval of full NDA applications. Even with the various protections in place, we may not be successful in securing or maintaining proprietary patent protection for our products and product candidates necessary to prevail should we need to bring any challenges under the above FDA regulatory structures. We may also not receive any anticipated periods of regulatory exclusivity. Competition that our products may face from biosimilar, interchangeable, generic, or 505 (b) (2) NDA products could materially and adversely impact our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates. In the United States, this risk has increased in recent years as the FDA and the U. S. government have taken steps to encourage increased drug and biologic competition in the market, in an effort to bring down the cost of pharmaceutical products. Commercialization of Translarna and Upstaza has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD or Upstaza for the treatment of AADC deficiency in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our business, results of operations, and financial condition. In some countries, particularly the member states of the EEA, the pricing of prescription pharmaceuticals is subject to strict governmental control. Each country in the EEA has its own pricing and reimbursement regulations and may have other regulations related to the marketing and sale of pharmaceutical products in the country. We generally will not be able to commence commercial sales of Translarna for the treatment of nmDMD or Upstaza for the treatment of AADC deficiency pursuant to the marketing authorization granted by the **EC** ~~European Commission~~ in any

particular member state of the EEA until we conclude the applicable pricing and reimbursement negotiations and comply with any licensing, employment or related regulatory requirements in that country. In some countries we may be required to conduct additional clinical trials or other studies of our product, including trials that compare the cost- effectiveness of our product to other available therapies in order to obtain reimbursement or pricing approval. We may not be able to conclude pricing and reimbursement negotiations or comply with additional regulatory requirements in the countries in which we seek to commercialize Translarna or Upstaza on a timely basis, or at all. The pricing and reimbursement process varies from country to country and can take a substantial amount of time from initiation to completion. Pricing negotiations may continue after reimbursement has been obtained. We cannot predict the ~~timing~~ **90timing** of Translarna' s or Upstaza' s commercial launch in countries where we are awaiting pricing and reimbursement guidelines. While we have submitted pricing and reimbursement dossiers with respect to Translarna for the treatment of nmDMD and Upstaza for the treatment of AADC deficiency in many EEA countries, we have only received both pricing and reimbursement approval on terms that are acceptable to us in a limited number of countries. The price that is approved by governmental authorities in any country pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under our reimbursed EAP programs and various forms of national " market access agreements " may need to be entered into to achieve reimbursement. In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payors. For example, in France, EAP and commercial sales of a product can begin while pricing and reimbursement rates are under discussion with the applicable government health programs. In the event that the negotiated price of the product is lower than the amount reimbursed for sales made prior to the conclusion of price negotiations, we may become obligated to repay such excess amount to the applicable government health program. We will make such retroactive reimbursement, if any, following the conclusion of price negotiations with the applicable government health authority. Further, based on unsustainable economics imposed by the arbitration board in Germany upon the conclusion of an arbitration process in 2016 with us and the German Federal Association of the Statutory Health Insurances, we delisted ~~96Translarna~~ -- **Translarna** from the German pharmacy ordering system, effective April 1, 2016. While some patients and healthcare professionals in Germany have been able to access Translarna through a reimbursed importation pathway possible under German law, there can be no assurance that other patients or healthcare professionals in Germany will be successful doing so or, if initially successful, that any or all will continue to be successful. We were required to reimburse payors in Germany the difference between the commercial price of Translarna and the price established by the arbitration board in Germany for sales made in Germany after December 2015, other than sales made pursuant to the reimbursed importation pathway. Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations and there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. In addition, adverse clinical and regulatory developments may exacerbate these risks. Reference pricing used by various EU member states and parallel distribution, or arbitrage between low- priced and high- priced member states, can further reduce prices and revenues. Publication of discounts by third- party payors or authorities may lead to further pressure on prices or reimbursement levels within the country of publication and other countries. If we fail to successfully secure and maintain pricing and reimbursement coverage for Translarna or Upstaza or are significantly delayed in doing so or if burdensome conditions are imposed by private payers, government authorities or other third- party payors on such reimbursement, planned launches in the affected countries will be delayed and our business, results of operations and financial condition could be adversely affected. Our relationships with customers, healthcare providers and professionals, patients, patient organizations, and third- party payors are or will be subject to applicable anti- kickback, fraud and abuse, transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Healthcare professionals and third- party payors play a primary role in the recommendation and prescription of any products or product candidates. Our arrangements with customers, healthcare professionals and third- party payors may expose us to broadly applicable fraud and abuse, transparency and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing authorization. Failure to maintain a comprehensive and effective compliance program, and to integrate the operations of any acquired businesses into a combined comprehensive and effective compliance program on a timely basis, could result in business practices and operations that expose us to a range of regulatory actions that could adversely affect our ability to commercialize our products and could harm or prevent sales of the affected products, or could substantially increase the costs and expenses of commercializing and marketing our products. ~~There~~ **91There** are numerous restrictions and reporting requirements under applicable U. S. federal and state healthcare laws and regulations, and equivalent laws and regulations in the EU and other countries in which we operate, as well as self- regulatory codes. Efforts to ensure that we and our business arrangements with third parties will comply with applicable healthcare laws, regulations, transparency requirements and self-regulatory codes have and will continue to involve substantial costs. We cannot guarantee that we, our employees, our consultants, our third- party contractors, or the healthcare professionals or entities with whom we expect to do business, are or will be in compliance with all federal, state and ex- U. S. regulations and codes. It is possible that governmental authorities could 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, exclusion from government funded healthcare programs, such as Medicare and Medicaid, reputational harm, and the curtailment or restructuring of our operations. Exclusion, suspension and debarment from government funded healthcare, procurement and non- procurement programs would adversely affect, perhaps materially, our ability to commercialize, sell or distribute any drug. Even if we were not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant time and resources and generate negative

publicity, which could also have an adverse effect on our business, financial condition and results of operations. ~~97Legislative~~ **Legislative** and regulatory changes affecting the pharmaceutical industry or the healthcare system more broadly may increase the difficulty and cost for us to obtain or maintain marketing authorization of and commercialize our products and product candidates and affect the coverage and reimbursement we may obtain. Our industry is highly regulated and changes in law may adversely impact our business, operations, or financial results. In the United States and some ex- U. S. jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing authorization of our products or product candidates, restrict or regulate post- approval activities and affect our ability to profitably sell any products or product candidates for which we have obtained, or may obtain, marketing authorization. Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of healthcare items and services. For example, in the United States, the Medicare Modernization Act requires manufacturers to calculate and report a drug' s Average Sales Price used to reimburse providers for physician- administered drugs under Medicare Part B and changed the way Medicare covers and pays for pharmaceutical products. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own policies. Therefore, any restrictions to coverage or reductions in reimbursement that result from the Medicare Modernization Act may result in a similar coverage restriction or reimbursement reduction from private payors. In addition, private payors may implement coverage restrictions or payment reductions independently from federal programs such as Medicare. Similarly, in the United States, the Affordable Care Act contains provisions that may reduce the profitability of drug products. However, legal challenges to the Affordable Care Act may contribute to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscore the potential for additional reform going forward. The Biden administration is expected to continue to take measures to further facilitate the implementation of the Affordable Care Act. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results. Promulgated and proposed regulatory changes could also affect coverage or reimbursement of our products and in 2016, CMS issued a final rule regarding the Medicaid drug rebate program, which among other things, revises the manner in which the " average manufacturer price " is to be calculated by manufacturers participating in the program and implements certain amendments to the Medicaid rebate statute created under the ACA. More recently, Congress amended the Medicaid statute, effective October 1, 2019, to exclude prices paid by secondary manufacturers for an authorized generic drug (but not a product approved under the BLA process) from the NDA holder' s AMP for the brand, thereby increasing the rebate amount and the 340B price for the brand. This was implemented by CMS in a final rule issued December 31, 2020. The rule also expanded the definition of products identified as " line extensions " and, in certain circumstances, required inclusion of patient copay assistance in Medicaid best price (effective January 1, 2023), thereby potentially increasing ~~Medicaid~~ **92Medicaid** rebates paid by manufacturers for such drugs. 340B program guidance regulations on civil monetary penalties for statutory violations, which had been finalized in early 2017 but deferred, recently also went into effect. In 2020, the Trump administration issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician- administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence- based care. More recently, on August 16, 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (**effective** beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program ~~98with~~ **with** a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single- source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high- cost drugs paid for by Medicare Part D **effective** starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated " maximum fair price " under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out- of- pocket drug costs at an estimated $ 4, 000 a year in 2024 and, thereafter beginning in 2025, at $ 2, 000 a year. We anticipate that the U. S. Congress, administrative agencies, state legislatures and the private sector will continue

to consider and may adopt healthcare policies intended to curb rising healthcare costs. These cost containment measures may include: ● controls on government funded reimbursement for drugs; ● caps or mandatory discounts under certain government sponsored programs; ● controls on healthcare providers; ● challenges to the pricing of drugs or limits on reimbursement of specific products through other means; ● reform of drug importation laws and policies; ● expansion of use of managed care systems in which the healthcare providers contract to provide comprehensive healthcare for a fixed cost per person; and ● requirements or restrictions related to direct- to- consumer advertising or drug marketing practices. We are unable to predict what additional legislation, regulations or policies, if any, relating to the healthcare industry or third- party coverage and reimbursement may be enacted in the future or what effect such legislation, regulations or policies would have on our business. In particular, we are unable to predict what changes the Biden administration will implement ~~through~~ **93through** the U. S. Congress or future executive orders and how these would impact us. Any cost containment measures, including those listed above, or other healthcare system reforms that are adopted, could significantly decrease the available coverage and the price we might establish for our products, which would have an adverse effect on our net revenues and operating results. Changes in FDA laws, regulations, and policies may also make it more difficult to obtain and maintain marketing authorizations. In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize Translarna, Upstaza and our product candidates. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. We cannot predict how future changes relating to healthcare reform in the EU, the United States, or other territories, will affect our business. Legislative and regulatory proposals have also been made to expand post- approval requirements, limit regulatory exclusivity periods or the applicability of such exclusivity periods, restrict sales and promotional activities for pharmaceutical products and to otherwise encourage competition in the market and bring down drug prices, including proposals related to drug importation. We cannot be sure whether additional legislative or regulatory changes will be enacted in any territory in which we are authorized, or become authorized, to market our products or product candidates, ~~99or~~ **or** whether applicable regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing authorizations of our products or product candidates, if any, may be. In addition, increased scrutiny by the U. S. Congress of the FDA' s approval process or by comparable ex- U. S. bodies overseeing regulatory authorities in other territories may significantly delay or prevent marketing authorization, as well as subject us to more stringent product labeling and post- marketing testing and other requirements. We cannot predict how future changes relating to pre- and post- marketing approval and requirements will affect our business. Risks Related to Our BusinessWe may expend our resources to pursue a particular product, 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. We focus on products, research programs and product candidates for specific indications. As a result, we may forgo or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. For example, in connection with our acquisition of Censa, we paid to the Censa securityholders (i) cash consideration of $ 15. 0 million, which consisted of an upfront payment of $ 10. 4 million and an additional $ 4. 6 million for the net assets on Censa ~~'~~ **'** s opening balance sheet as of the date of the acquisition, and (ii) 845, 364 shares of our common stock. Censa securityholders may also be entitled to receive contingent consideration payments from us in the future **. For example, we expect to make payments to the former Censa securityholders of $ 65. 0 million in the aggregate in cash upon the potential achievement in 2024 of regulatory milestones relating to sepiapterin pursuant to the Censa Merger Agreement** . We may never realize the anticipated benefits of the acquisition of Censa and by investing our resources in sepiapterin, we may be required to forgo or delay other opportunities. In addition, we have previously commenced clinical trials that were not successful for a number of reasons, including inconsistent or negative data and difficulties identifying qualified patients. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. Notwithstanding our large investments to date and anticipated future expenditures in proprietary technologies for ~~both~~ small- molecule ~~and gene therapy~~ drug discovery, to date we have been granted marketing authorization for a limited number of commercial products and have not achieved profitability. We may never realize a return on investment. We may not be able to successfully renew or satisfy the ongoing requirements of our current marketing authorizations for our current products and we may never successfully develop any other marketable drugs or indications using our scientific approach. As a result of pursuing the development of product candidates using our proprietary technologies, we may fail to develop product ~~candidates~~ **94candidates** or address indications based on other scientific approaches that may offer greater commercial potential or for which there is a greater likelihood of success. Research programs to identify new product candidates require substantial technical, financial and human resources. These research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development. **For example, in May 2023, as part of our strategic portfolio prioritization, we decided to discontinue our preclinical and early research programs in our gene therapy platform, which included programs for Friedreich ataxia and Angelman syndrome, after previous significant investments in these programs.** 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. We ~~face risks related to health epidemics and other widespread outbreaks of contagious disease, which have previously, and may once again, delay our ability to complete our ongoing clinical trials and initiate future clinical trials, disrupt regulatory activities and have other adverse effects on our business and operations, including the novel coronavirus (COVID- 19) pandemic, which disrupted, and may continue to disrupt, our operations and may significantly impact our operating results. In addition, the COVID- 19 pandemic has caused substantial disruption in the financial markets and economies, which could result in adverse effects on our business and operations.~~

Significant outbreaks of contagious diseases, and other adverse public health developments, could have a material impact on our business operations and operating results. In December 2019, a strain of novel coronavirus, COVID- 19, causing 100respiratory illness emerged in the city of Wuhan in the Hubei province of China. Since that time, multiple other countries throughout the world, including the United States, have been affected by the spread of the virus. To date, responsive measures such as social distancing, vaccine mandates, travel bans and quarantines have been put into place in many countries throughout the world, including the United States. These responsive measures have had a significant impact, both direct and indirect, on business and commerce worldwide, as worker shortages have occurred, supply chains have been disrupted and facilities and production have been suspended or curtailed. The spread of COVID- 19 and the responsive measures taken to date have limited our access to our facilities, the access of trial participants to clinical sites and, at one point in time, caused the majority of our employees to work from home. We continue to monitor the global spread and response of international, national and local authorities of COVID- 19 and have put in place and will continue to put in place measures as appropriate and necessary for our business and the safety of our employees. While we expect the pandemic to continue to have an adverse effect on our business and operations, and the pandemic may have an adverse effect on our financial condition and results of operations, we are unable to predict the extent or nature of the future progression of the COVID- 19 pandemic or its effects on our business, operations, financial condition and results of operations at this time. Furthermore, we have clinical trial sites located in countries that have been affected by COVID- 19 that have been and may continue to be disrupted, including the United States. The disruption of our clinical trial sites has had an adverse impact on our clinical trial plans and timelines. The COVID- 19 pandemic has also adversely affected our ability to timely enroll patients for our clinical trials which may delay the completion of clinical trials. For example, we previously experienced delays in enrolling our registration- directed Phase 2 / 3 randomized, placebo- controlled trial of vatiquinone in children with mitochondrial disease associated seizures as some patients were unable or hesitant to travel to clinical trial sites due to the COVID- 19 pandemic. We anticipate results from the Phase 2 / 3 trial to be available in the second quarter of 2023. Such disruptions could result in significant delays or could require us to abandon a clinical trial altogether. For additional information, see the risk factor under " Risks Related to the Development and Commercialization of our Products and our Product Candidates " titled, " If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented. " Our ability to market and promote our products, as well as patient demand for our products may also be impacted. Because access to healthcare providers and institutions has been limited in certain regions of the world, we have had to transition to virtual and online promotion to reach existing and potential customers in those areas. Healthcare provider and institution restrictions and closures, as well as patient reticence to visit their physicians may also result in a decrease in product prescribing. Significant suppliers and manufacturing located in countries that have been affected by COVID- 19 may also be disrupted, which may affect our ability to procure items that are essential for our research and development activities and may cause disruptions or delays in our sales and commercialization efforts of approved products and clinical trials with respect to product candidates. For example, in response to the COVID- 19 pandemic, China has at times imposed complete lockdowns of cities that have experienced a high number of COVID- 19 cases. We contract with third- party manufacturers located in China that may be forced to shut down for an unknown amount of time if the Chinese government determines that there is a COVID- 19 outbreak where they are located. Additionally, we have experienced delays in certain of our preclinical programs due to a shortage in non- human primates. Many manufacturers have also experienced shortages of key equipment and ingredients needed for product manufacturing. The response to the COVID- 19 pandemic may also redirect resources with respect to regulatory matters in a way that would adversely impact our ability to progress to regulatory approval. In response to the global uncertainty caused by the COVID- 19 pandemic, we may also choose to redirect our own resources in a way that may adversely impact or delay certain of our programs. Furthermore, we may face impediments to regulatory meetings and approvals due to measures intended to limit in- person interactions. For example, due to delays related to responsive measures to the COVID- 19 pandemic taken in Europe in 2021, including travel bans and quarantines, the CHMP required additional time to complete its pre- approval inspections and imposed a clock- stop extension with respect to our MAA for the treatment of AADC deficiency in the EEA. To the extent that inspections of facilities by governmental authorities are required, the review of our marketing applications or supplements may further be delayed as regulatory authorities, such as FDA, have significantly limited facility inspections during the pandemic. 101We cannot predict the severity and duration of future COVID- 19 outbreaks or other widespread outbreaks of contagious diseases. If COVID- 19 outbreaks or other outbreaks are not effectively and timely controlled, we may experience further or prolonged disruption of our clinical trials, third- party suppliers or contract manufacturers, extended closures of facilities, such as clinical trial sites, suppliers, manufacturers and distributors, including single source suppliers, and further delays with respect to regulatory approvals or the commercialization of any current or future products. Such events may materially and adversely affect our business operations and financial condition. Additionally, the COVID- 19 pandemic has caused significant disruptions in the financial markets, and may continue to cause such disruptions, which could impact our ability to raise additional funds and has also impacted, and may continue to impact, the volatility of our stock price and trading in our stock. Moreover, the COVID- 19 pandemic has significantly impacted economies worldwide, which could result in adverse effects on our business and operations. We cannot be certain what the overall impact of the COVID- 19 pandemic or other future potential outbreaks of contagious diseases will have on our business and their potential to materially adversely affect our business, financial condition, results of operations, and prospects. We contract with third parties for the manufacture and distribution of our products and certain of our product candidates, which may increase the risk that we will not have sufficient quantities of our products or product candidates, such quantities may not meet the applicable regulatory quality standards, or such quantities at an acceptable cost, which could delay, prevent or impair our commercialization or development efforts. For certain of our product candidates, we may also directly engage in manufacturing, which will require significant expenditures and compliance with the FDA' s manufacturing requirements. We have limited personnel with experience in drug manufacturing and currently rely on third parties to manufacture our products and certain

product candidates on a clinical or commercial scale. We currently rely on third parties for supply of the active pharmaceutical ingredients used in all of our products and product candidates. We outsource most of the manufacturing, packaging, labeling and distribution of our products and certain of our product candidates to third parties, including our commercial supply of Translarna, Emflaza and Upstaza. **Additionally** ~~In 2021~~ , we ~~began cGMP manufacturing of clinical material at the Hopewell Facility for certain of our gene therapy product candidates. We also~~ utilize the Hopewell Facility to produce plasmid DNA and AAV vectors for gene therapy applications for external customers ~~. We still rely on third- party manufacturers to complete product testing for all of our gene therapy product candidates that we manufacture at the Hopewell Facility as well as to provide sufficient quantities of certain program materials that we have not yet transitioned to Hopewell~~ . With respect to the Hopewell Facility, we are required to directly comply with the applicable regulatory authorities' manufacturing requirements and are subject to inspection in the same way that our contract manufacturers are ~~. Utilizing our own manufacturing will require a significant continued investment and we may not be successful in maintaining our own manufacturing capacity, especially given the complexities of gene therapy manufacturing~~ . For additional information, see the risk factor under " Risks Related to the Development and Commercialization of our Products and Product Candidates " titled, " Certain of our products and product candidates, such as our gene therapies and other biologic product candidates, may be difficult to produce, presenting manufacturing challenges that may delay product development and regulatory approval. " We do not directly control manufacturing for ~~most of~~ our products and product candidates and we are dependent on and will continue to be dependent on, our contract manufacturers for compliance with cGMP or good distribution practice, or GDP, or similar regulatory requirements outside the EU and the United States for manufacture of both active drug substances and finished drug products. Should we or our contract manufacturers fail to comply with these requirements, we and they could face significant regulatory and commercial consequences. For example, regulatory authorities routinely inspect manufacturing and other drug / biologic facilities. Our manufacturers and manufacturing facilities must also be approved by such regulatory authorities pursuant to inspections that will be conducted after we submit our marketing applications and will be subject to continuing regulatory authority inspections should we receive marketing approval. If ~~we or~~ our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the EU member state regulatory authorities, FDA, or other ex- U. S. regulatory agencies, ~~we or~~ they will not be able to secure and / or maintain regulatory approval for the manufacturing facilities, and we would not be able to secure and / or maintain, or may be delayed in securing regulatory approval of marketing applications or supplements for the applicable products or product candidates. In addition, we or third-party manufacturers or distributors may not be able to comply with generally accepted worker safety standards, cGMP, GDP or similar regulatory requirements outside the EU and the United States. Our failure, or the failure of our third- party manufacturers or distributors, over whom we have no direct control, to comply with applicable regulations could result in sanctions being ~~102imposed~~ --- **imposed** on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, clinical holds or termination of clinical studies, warning or untitled letters, regulatory communications warning the public about safety issues with a product, import or export refusals, license revocation, seizures, detentions, or recalls of product candidates or ~~product~~ **products** , operating restrictions, criminal prosecutions or debarment, suits under the civil False Claims act, corporate integrity agreements, or consent decrees, any of which could significantly and adversely affect our reputation and supplies of our products or product candidates and our business, results of operations and financial condition could be materially adversely affected. ~~In~~ **95In** addition, we have no direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our contract manufacturers are engaged with other companies to supply and / or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such other materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may generally affect the regulatory status of our contract manufacturers' facilities **and our products or product candidates** . If the FDA, EU member state regulatory authorities or a comparable ex- U. S. regulatory agency do not approve these or our facilities for the manufacture of our products or product candidates or if it withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would negatively impact our ability to develop, obtain regulatory approval for or market our products or product candidates, if approved. There is also no guarantee that we would be able to find alternative manufacturing facilities or enter into agreements with alternative manufacturers on favorable terms. There may be limited manufacturers who would have the ability to manufacture our products and product candidates, especially our gene therapy product candidates, particularly as the pharmaceutical manufacturing industry becomes increasingly more consolidated. ~~To the extent that we decide to manufacture our own clinical and commercial supply of Upstaza as an alternative source of supply, there is no guarantee that we will be able to cost- effectively produce sufficient quantities of our program materials.~~ Moreover, any alternative manufacturers would need to be approved by the relevant regulatory authority, which approval is not guaranteed. We, accordingly, may not be able to make alternative manufacturing arrangements, which could adversely affect our products, product candidates, and our business, results of operations and financial condition. See " Item 1. Business — Manufacturing " for additional information regarding the manufacturing of our products and product candidates. Even if we are able to establish and maintain arrangements with third-party manufacturers, distributors and other third parties, reliance on such third parties entails additional risks, including: ● reliance on the third party for regulatory compliance and quality assurance; ● the possible breach of the agreements by the third party; ● the possible misappropriation of our proprietary information, including our trade secrets and know- how; ● the possibility of commercial supplies of our products not being distributed to commercial vendors or end users in a timely manner, resulting in lost sales; ● the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions; ● the possibility of third- party resources not being devoted in the manner necessary to satisfy our requirements within the expected time frame; ● the possibility of third parties not providing us with accurate or timely information regarding their inventories, the number of patients who are using our products, or serious adverse events and / or product complaints

regarding our products; ● the possibility of third parties being unable to satisfy their financial obligations to us or to others; and ● the possible termination or nonrenewal of a critical agreement by the third party at a time that is costly or inconvenient to us. Many additional factors could cause production or distribution interruptions with the manufacture and distribution of any of our products and product candidates, including human error, natural disasters, labor disputes, acts of terrorism or war, equipment malfunctions, contamination, supply chain disruption, including disruptions caused by ~~the~~ **outbreaks of contagious disease, such as** COVID- 19 ~~pandemic~~, or raw material and component shortages. We have previously experienced delays in receiving certain raw materials in connection with supply chain disruptions caused by the COVID- 19 pandemic, however, these delays did not affect or delay our manufacturing given our inventories for such materials at the time. If future supply chain disruptions ~~103create~~ --- **create** prolonged delays, the supplies of our products or products candidates may be significantly and adversely affected and our business, results of operations and financial condition could be materially adversely affected. Our products and product candidates and any other products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. In addition, changes in cGMP regulations could negatively impact our ability or the ability of our contract manufacturers to complete the manufacturing process of our products and our product candidates in a compliant manner on the schedule we require for commercial and clinical trial use, respectively. ~~If~~ **96If** we or the third parties that we engage to manufacture product for our commercial sales, preclinical tests and clinical trials should, prior to the time that we have validated alternative providers, cease to continue to do so for any reason, we likely would experience delays in our ability to supply our products or product candidates to patients or in our ability to advance our clinical trials while we identify and qualify replacement suppliers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our products or product candidates or the drug substances used to manufacture them, we will lose commercial sales revenue and it will be more difficult for us to develop our product candidates and compete effectively. In addition, to the extent that any contract manufactures that we engage develop proprietary manufacturing processes or procedures, should we need to change manufacturers, we may not be able to transfer know- how to a new manufacturer. In such a case, the new manufacturer would need to invest substantial time, money, and effort to develop its own processes and procedures, which would require regulatory authority approval. Third parties might illegally distribute and sell counterfeit or unfit versions of our products that do not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit drug may be at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit drugs sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in- transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, our reputation and our business. Our current and anticipated future dependence upon others for the manufacture and distribution of Translarna, Emflaza, Upstaza, Tegsedi, Waylivra and ~~certain of~~ our product candidates may adversely affect our business, financial condition, results of operations and limit our ability to grow including our ability to develop product candidates and commercialize our products that receive regulatory approval on a timely and competitive basis. We rely on third parties to conduct our preclinical and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials. We do not independently conduct preclinical or clinical trials for our products or product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to perform this function. While we have agreements governing the activities of such third parties, we have limited influence and control over their actual performance and activities. For instance, our third- party service providers are not our employees, and except for remedies available to us under our agreements with such third parties we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non- clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements or for other reasons, our trials may be repeated, extended, delayed, or terminated, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates, we may not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third- party service providers in the future, our ~~104business~~ --- **business** may be materially and adversely affected. Further, any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it will delay our product development activities. Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. **We are required to monitor the activities of these third parties but our monitoring may not be able to detect any existing or emerging issues.** Moreover, the FDA requires us to comply with standards, commonly referred to as GCP for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government- sponsored database, ClinicalTrials. gov, within certain timeframes. Failure to ~~do~~ **97do** so can result in fines, adverse publicity and civil and criminal sanctions. In addition, we will be required to report certain financial interests of our third- party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA or comparable ex- U. S. regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who may have conflicts of interest. We must further ensure that our preclinical trials are conducted in accordance with good

laboratory practices, or GLPs, as appropriate. Regulatory authorities enforce these requirements through periodic inspections or remote regulatory assessments of trial sponsors, clinical and preclinical investigators, and trial sites. Similar GCP and transparency requirements apply in the EU. Failure to comply with the applicable regulatory requirements, including with respect to clinical trials conducted outside the EU and United States, can also lead regulatory authorities to refuse to accept into account clinical trial data submitted as part of a marketing application, as well as other regulatory consequences, as further described above. Furthermore, third parties that we rely on for our clinical development activities may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing authorizations for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Our product development costs will increase if we experience delays in testing or obtaining marketing authorizations. We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing authorizations of our products or product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue. We currently depend, and expect to continue to depend, on collaborations with third parties for the development and commercialization of some of our products and product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these products and product candidates. For each of our product candidates, we plan to evaluate the merits of retaining commercialization rights for ourselves or entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies, such as our collaborations with Roche and the SMA Foundation, for our spinal muscular atrophy program, including Evrysdi. We have entered into arrangements with certain third parties to market or distribute Translarna for the treatment of nmDMD in certain countries and, as we continue to implement our commercialization plans for Translarna, we anticipate that we will engage additional third parties to perform these functions for us in other countries. We generally plan to seek collaborators for the development and commercialization of product candidates that have high anticipated development costs, are directed at indications for which a potential collaborator has a particular expertise, or involve markets that require a large sales and marketing organization to serve effectively. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements may include: large and mid- size pharmaceutical companies, regional and national pharmaceutical companies and / or biotechnology companies. We will have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates and our collaborators will be subject to the same product development and commercialization risks that we are subject to. Our ability to generate revenues from these arrangements will depend on our collaborators' desire and ability to successfully perform the functions assigned to them in these arrangements **in a compliant manner**. In particular, the commercial success of Evrysdi will depend on the success of Roche' s commercialization program. ~~105Furthermore~~ --- **Furthermore**, the successful development of another product candidate from our spinal muscular atrophy program will depend on the success of our collaborations with the SMA Foundation and Roche, including whether Roche pursues clinical development of any other compounds identified under the collaborations. Collaborations involving our products and product candidates, including our collaborations with the SMA Foundation and Roche, pose the following risks to us: ● collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations; **98** ● collaborators may not pursue development and commercialization of our products and product candidates or may elect not to continue or renew development or commercialization programs, based on 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 replace or compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; ● collaborators may fail to comply with the applicable regulatory requirements, subjecting them or us to potential regulatory enforcement action; ● a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products; ● collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; ● collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; ● disputes may arise between the collaborator and us as to the ownership of intellectual property arising during the collaboration; ● we may grant exclusive rights for our products or product candidates to our collaborators, which would prevent us from collaborating with others, or from using our products or product candidates ourselves; ● disputes may arise between the collaborators and us that result in the delay or termination of the collaboration, which may include ending research, development or commercialization activities for our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and ● collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates. Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. 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. We may rely on third parties to perform many essential services for any products that we commercialize, including services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, cash collection, and pharmacovigilance and adverse event reporting. If

these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize our product candidates will be significantly impacted and we may be subject to regulatory sanctions. We may retain third- party service providers to perform a variety of functions related to the sale and distribution of our product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to warehousing and inventory control, distribution, customer service, accounts receivable management, and cash collection. If we retain a service provider, we will substantially rely on it as well as other third- party providers that perform ~~106services~~ **services** for us, including entrusting our inventories of products to their care and handling. If these third- party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action. In addition, we may engage third parties to perform various other services for us relating to pharmacovigilance and adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements, we could be subject to regulatory sanctions. ~~Additionally~~ **99Additionally** , we may contract with a third party to calculate and report pricing information mandated by various government programs. If a third party fails to timely report or adjust prices as required, or errors in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability, and potentially subject us to regulatory sanctions or False Claims Act lawsuits. Our business and operations would suffer in the event of computer system failures, cyber- attacks or a deficiency in our, or our collaborators' or third- party vendors', cyber- security. We collect, store and transmit large amounts of confidential information, including personal information, operational and financial transactions and records, clinical trial data and information relating to intellectual property, on internal information systems and through the information systems of collaborators and third- party vendors with whom we contract. Despite our implementation of security measures, including implementing the National Institute of Standards and Technology cybersecurity framework, instituting a training and compliance program on cybersecurity for all employees and doing a yearly external audit and penetration test, these information systems are vulnerable to damage from computer viruses, malware, **ransomware,** natural disasters, terrorism, war, telecommunication and electrical failures, cyber- attacks or cyber- intrusions over the Internet or other mechanisms, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. No such security measures can eliminate the possibility of the information systems' improper functioning or the improper access or disclosure of confidential or personally identifiable information such as in the event of cyber- attacks. ~~The risk of a security~~ **Cybersecurity** ~~breach or disruption, particularly through cyber-~~ **related risks have** ~~attacks or cyber- intrusion, including by computer hackers, criminals, ex- U. S. governments, and cyber terrorists, has~~ generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. Additionally, outside parties may attempt to fraudulently induce employees, collaborators, or other third- party vendors to disclose sensitive information or take other actions, including making fraudulent payments or downloading malware, by using " spoofing " and " phishing " emails or other types of attacks. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our clinical and commercialization activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy, despite our having a security risk insurance policy and disaster recovery and incident response plans. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach was to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur material legal claims and liability, damage to our reputation, suffer loss or harm to our intellectual property rights, face significant financial exposure, including incurring significant costs to remediate possible injury to the affected parties and the further research, development and commercial efforts of our products and product candidates could be delayed. Product liability and other civil lawsuits against us could cause us to incur substantial liabilities and to limit clinical trials or commercialization of any current or future products. Our insurance program may not be extensive enough to adequately protect us against these risks. We face an inherent risk of product liability exposure related to the commercialization of our products and any product candidate that we may market or commercialize, any gene therapy product materials that we manufacture for third parties at the Hopewell Facility and in connection with the human clinical trials testing of our products and product candidates. If we cannot successfully defend ourselves against claims that our product candidates, products or gene therapy product ~~107materials~~ **materials** caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in: ● reduced resources of our management to pursue our business strategy; ● decreased demand for our products or any product candidates that we may develop; ● decreased demand for the gene therapy product materials that we manufacture for third parties at the Hopewell Facility; ● injury to our reputation and significant negative media attention; ● the inability to continue current clinical trials or begin planned clinical trials; ● withdrawal or reduced enrollment of clinical trial participants; ● significant costs to defend the related claims / litigation; ● increased insurance costs, or an inability to maintain appropriate insurance coverage; **100** ● substantial monetary awards to trial participants, patients and / or their families; ● loss of revenue; ● the inability to commercialize or to continue commercializing any products or product candidates; ● initiation of investigations and enforcement actions by regulators; and ● the withdrawal of products from the market, product recalls, or the cessation of development or regulatory disapproval of product candidates or withdrawal of approvals, as well as labeling, marketing, or promotional restrictions. We have a broad insurance program covering risks appropriate to our research and development activities, clinical programs, and aggregate annual limits of $ 25. 0 million covering our products and sales. We also have industry standard insurance policies covering other aspects of our business and operations based on our locations, activities and other relevant factors. With respect to all insurance matters, we are advised by our insurance brokers and our insurance advisor,

who we retain and compensate on a non- commission basis. However, our insurance program may not adequately cover the risks that we face for a variety of reasons, including: ● certain risks and related losses, such as delays to our clinical and development programs, are too speculative or unquantifiable for us to adequately insure against; ● if we were to face multiple claims, renewing or replacing our insurance may become more expensive, the terms (including deductibles and limits) we receive may worsen, and we may even have difficulty securing any coverage at all; ● our insurance limits may not be adequate to cover all liabilities and defense costs that we may incur; and ● we may need to further increase our insurance coverage if we commercialize our current products in additional jurisdictions, our sales increase, or we commercialize new products. The cost of insurance coverage is highly variable, based on a wide range of factors. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability or defense costs that may arise. In addition, we could be subject to other costly civil litigation, including contractual claims with respect to our expected manufacturing of gene therapy product materials for potential external customers. If our customers believe that we have violated our contractual terms, they may seek reimbursement for the cost of our gene therapy product materials or other related losses, the cost of which could be significant. If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business. We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures, manufacturing and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations currently, and may in the future, involve the use of hazardous and flammable materials, including chemicals and medical and biological materials, and produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we cannot eliminate the risk of contamination or injury from these materials. In the ~~108event~~ --- **event** of contamination or injury resulting from our use of hazardous materials or disposal of hazardous wastes, we could be held liable for any resulting damages, and any liability could exceed our resources. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or manufacturing and distribution efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel. We are highly dependent on Dr. **Matthew Klein** ~~Stuart W. Peltz~~ , our ~~co- founder and~~ Chief Executive Officer, and the other principal members of our executive, commercial and scientific teams. Although we have formal employment agreements with each of our executive ~~officers~~ **101officers** , these agreements do not prevent our executives from terminating their employment with us at any time. We do not maintain " key person " insurance on any of our executive officers. The loss of the services of any of these persons might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. ~~Additionally, because the field of gene therapies and gene therapy manufacturing is new and complex, we might face a shortage of skilled individuals with substantial gene therapy and gene therapy manufacturing experience. As a result, competition for skilled personnel, including in gene therapy research and gene therapy manufacturing, is intense and the turnover rate can be high.~~ We ~~may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also~~ experience competition for the hiring of scientific and clinical personnel from **numerous pharmaceutical and biotechnology companies as well as** universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. ~~We are in the process of expanding our development, regulatory, and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. In connection with our commercialization plans and business strategy, including our continued commercialization of Translarna, Emflaza, Upstaza, Tegsedi and Waylivra and, if approved, other product candidates, we have experienced and may to continue to experience significant growth in our employee base for sales, marketing, operational, managerial, financial, human resources, drug development, quality, regulatory and medical affairs and other areas. This growth has imposed and will continue to impose significant added responsibilities on members of management, including the need to recruit, hire, retain, motivate and integrate additional employees, including employees who joined us in connection with any of our acquisitions or other strategic transactions. Also, our management may have to divert a disproportionate amount of its attention away from our day- to- day activities and devote a substantial amount of time to managing these growth activities, including any applicable integration. To manage our recent and anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. In addition, we may need to adjust the size of our workforce as a result of changes to our expectations for our business, which can result in diversion of management attention, disruptions to our business, and related expenses. For example, following our receipt of the Refuse to File letter from the FDA in 2016, we implemented a reorganization of our operations in March 2016 that resulted in a one- time charge for the related work- force reduction. The physical 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. 109Risks~~ --- **Risks** Related to our Intellectual PropertyIf we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be adversely affected. Our success depends in large part on our ability to obtain and maintain patent protection

or other intellectual property rights with respect to our proprietary technology and products. One primary way that we seek to protect our proprietary position is by filing patent applications in the United States and in certain ex- U. S. jurisdictions related to our proprietary technology and products. This process is expensive and time- consuming, and we may not be able to file and prosecute all necessary or desirable patent applications. It is also possible that we will fail to file a patent application on patentable aspects of our research and development. Moreover, if we license technology or product candidates from third parties, these license agreements may not permit us to control the filing and prosecution of patent applications, or to maintain or enforce the patents. These agreements could also give our licensors the right to enforce the licensed patents without our involvement, or to decide not to enforce the patents at all. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which prevent others from commercializing competitive technologies and products. Changes in patent laws or their interpretation in the United States and other countries may diminish the value of our patents. The laws of ex- U. S. countries may not protect our rights to the same extent as the laws of the United States. For example, patent law in many countries restricts the patentability of methods of treatment of the human body more than U. S. law does. In addition, we may not pursue or obtain or be able to pursue or obtain patent protection in all major markets. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In addition, the Leahy- Smith America Invents Act of 2011, or the Act, which reformed certain patent laws in the U. S., may create additional uncertainty. The significant changes engendered by the Act include switching from a " first- to- invent " system to a " first- to- file " system, and the implementation of new procedures that permit competitors to challenge our patents in the USPTO after grant, including inter partes review and post grant review. Moreover, we may be subject to a third party prior art submissions in a patent office, or may become involved in patent office proceedings, including oppositions, derivation proceedings, reexamination, inter partes review, post grant review, interference proceedings, or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with ~~us~~ **102us** , without payment to us, or result in our inability to manufacture or commercialize products without infringing third- party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection or prevent competitors from competing with us. Our competitors may be able to circumvent our owned or licensed patents by developing alternative technologies or products in a non- infringing manner. Other companies may also attempt to circumvent any regulatory data protection or market exclusivity that we obtain under applicable legislation, which may require us to allocate significant resources to prevent such circumvention. Legal and regulatory developments in the European Union, or EU, and elsewhere may also result in clinical trial data and other information, that would ordinarily be treated as trade secret, submitted as part of a marketing authorization application becoming publicly available. ~~110The~~ **The** EMA Policy on publication of clinical data and other such information, as well as the current application of EU freedom of information regulations, could impact our proprietary information (comprising both clinical and non- clinical data and other information) that would normally be maintained by a regulatory body as commercially confidential. Such developments could enable other companies to circumvent our intellectual property rights and use our clinical trial data or other information to obtain marketing authorizations in the EU and in other jurisdictions where we have not been able to obtain any intellectual property or regulatory protection, resulting in loss of market share. Such developments may also require us to allocate significant resources or engage in litigation to prevent other companies from circumventing or violating our intellectual property rights. Our attempts to prevent third parties from circumventing or violating our intellectual property and other rights may ultimately be unsuccessful. We may also fail to take the required actions to maintain our patents. For example, during 2015, we were notified by the EMA that it had received from another pharmaceutical company a request under Regulation (EC) No 1049 / 2001 seeking access to aspects of our marketing authorization for Translarna for the treatment of nmDMD. Following the decision of the EMA to release such documentation with only minimal redactions we initiated litigation before the General Court of the EU to prevent disclosure of this information. In the first quarter of 2018, the Court ruled in favor of the EMA, allowing the EMA to release the documentation. We appealed the General Court' s decision to the Court of Justice of the EU, or CJEU, but the CJEU dismissed our appeal in January 2020 and released the information to the requester. An issued patent may be challenged, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful. Competitors may infringe our intellectual property. To counter infringement or unauthorized use, we may be required to file a lawsuit and claims for damages, which can be expensive and time consuming. Any claims we

assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property or defenses, such that they do not infringe our intellectual property or that our intellectual property is invalid or unenforceable. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent' s claims narrowly or may refuse to stop the other party from using the technology at issue. ~~Third~~ **103Third** parties may initiate legal proceedings alleging that our patents are invalid and unenforceable or that we are infringing their intellectual property rights, 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 products and our product candidates and use our proprietary technologies without infringing the intellectual property and other proprietary rights of third parties. We may not be aware of all intellectual property rights potentially relating to our product and our product candidates. Typically, patent applications in the United States and other jurisdictions are not published until 18 months after filing, or in some cases not at all, and new patent applications are continuously publishing. Thus, we may not be aware of patents or patent applications relating to our product or our product candidates. There may be pending or future patent applications that, if issued, would block us from commercializing our products. Thus, we do not know with certainty whether any of our products or product candidates, or our commercialization thereof, would or would not infringe any third party' s intellectual property. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights or other proprietary with respect to our products and technology. Third parties may assert infringement claims ~~111against~~ **against** us based on existing or future intellectual property rights. We may allege that a third party patent we are alleged to infringe is invalid and / or we may be able to avail ourselves in the United States of the safe harbor exemption provided by the Hatch- Waxman Act as a basis for non-infringement. In order to successfully challenge the validity of a third party issued U. S. patent that we are alleged to infringe, we would need to overcome that patent' s presumption of validity in district court or prove unpatentability by a preponderance of the evidence before the USPTO in a post grant proceeding. There is no assurance that a court or the USPTO would find these claims to be invalid or unpatentable, respectively. If we are found to infringe a third party' s intellectual property rights, or in order to avoid or settle litigation, we may seek to obtain a license 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. Also, any license obtained may be non- exclusive, thereby giving our competitors access to the same technologies licensed to us, and could require us to make substantial payments. We could be forced, including by court order, to cease commercializing an alleged infringing technology or product. In addition, we could be found liable for monetary damages if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from commercializing our products or our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property. Many of our employees were previously employed at universities or other companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property of any such employee' s former employer. Litigation may be necessary to defend against these claims. In addition, while we typically require our employees and contractors who may be involved in the 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 develops intellectual property that we regard as our own. Our and their assignment agreements may not be self- executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management. ~~Intellectual~~ **104Intellectual** property litigation could cause us to spend substantial resources and could distract our personnel from their normal responsibilities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of such proceedings. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, sales, marketing or distribution activities. We may not have sufficient resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Without patent protection, our marketed products may face generic competition. Certain of the products we market have no or limited patent protection and, as a result, potential competitors face fewer regulatory barriers in introducing competing products. Without patent protection or other regulatory exclusivity, we may ~~112not~~ **not** be able to exclude others from, among other things, selling or importing similar products in any jurisdiction. In some instances, we may rely on trade secrets and other unpatented proprietary information to protect our commercial position, although we may be unable to provide adequate protection for our commercial position via these means. In other instances, we may need to rely on regulatory exclusivity to protect our commercial position. Furthermore, generic competition against a branded product often results in decreases in the prices at which the branded product can be sold, particularly when there is more than one generic product available in the marketplace. Third- party companies could also develop products that are similar, but not identical, to our marketed products, such as an

alternative formulation of our product or an alternative formulation combined with a different delivery technology, and seek approval in the United States by referencing our products and relying, to some degree, on the FDA' s finding that our products are safe and effective in their approved indications. In addition, legislation enacted in the United States allows for, and in a few instances, in the absence of specific instructions from the prescribing physician, mandates the dispensing of generic products rather than branded products where a generic version is available. On February 9, 2017, the FDA approved the corticosteroid Emflaza for the treatment of patients 5 years and older with DMD. Although approved for other indications outside of the United States, this was the first approval for deflazacort in the United States and the first approval in the United States for the use of a corticosteroid to treat DMD. **We have previously relied on this exclusivity period to commercialize Emflaza in the United States.** Emflaza' s seven- year period of orphan drug exclusivity related to the treatment of DMD in patients five years and older ~~expires~~ **expired** in February 2024 **. We expect the expiration of this orphan drug exclusivity to have a significant negative impact on Emflaza net product revenue** . Emflaza' s orphan drug exclusivity related to the treatment of DMD in patients two years of age to less than five expires in June 2026. We ~~rely on regulatory exclusivity for Emflaza and~~ currently have no issued patents that could prevent a third- party company from seeking to introduce a generic Emflaza formulation in the United States for the treatment of DMD or another indication, and we ~~may never~~ **do not expect to** be able to obtain such patent protection. Such third- party companies may also obtain patents covering a new deflazacort formulation or method of use. If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed. In addition to seeking patents and regulatory exclusivity for some of our technology and products, we also rely on trade secrets, including unpatented know- how, technology and other proprietary information, to maintain our competitive position. More particularly, we may rely on trade secrets and other unpatented proprietary information to protect our competitive position related to our products and product candidates, especially when patent protection is not obtainable. We seek to protect these trade secrets, in part, by entering into non- disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors, partners and other third parties. We also enter into confidentiality and invention or ~~patent~~ **105patent** assignment agreements with our employees and consultants. However, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets or that the agreements we have executed will provide adequate protection. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time- consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, 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 any of our trade secrets were to be obtained or independently developed by a competitor, our competitive position would be harmed. If our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, employees, consultants, advisors, partners and other third parties develop new inventions or processes related to our products independently, or jointly with us, that may be applicable to our products under development, disputes may arise about ownership or proprietary rights to those inventions and processes. Enforcing a claim that a third party illegally obtained and is using any of our inventions or trade secrets is expensive and time- consuming, and the outcome is unpredictable. In addition, courts outside of the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know- how. ~~113We~~ **We** have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business. Our trademark applications may be refused registration, or our registered trademarks may not be maintained or may be found to be unenforceable. During trademark examination proceedings, our trademark applications may be rejected. Although we are given an opportunity to respond to those rejections in most jurisdictions, we may not be able to successfully overcome them. In addition, in the U. S. Patent and Trademark Office and Trademark Offices in many other jurisdictions, third parties are given an opportunity to oppose pending trademark applications or to seek cancellation of registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Further, if we do not secure registrations for our trademarks, we may encounter difficulty enforcing our trademark rights against third parties in the jurisdictions where we do not have registered rights. If we are not able to obtain adequate trademark protection or regulatory approval for our brand names, we may be required to re- brand affected products, which could cause delays in getting such products to market and substantially increase our costs. To protect our rights in any trademark we intend to use for our products or product candidates, we may seek to register such trademarks. Trademark registration is territory- specific and we must apply for trademark registration in the United States as well as any other country where we intend to commercialize our product or product candidates. Failure to obtain trademark registrations may place our use of the trademarks at risk or make them subject to legal challenges, which could force us to choose alternative names for our product or product candidates. In addition, the FDA, and other regulatory authorities outside the United States, conduct an independent review of proposed product names for pharmaceuticals, including an evaluation of the potential for confusion with other pharmaceutical product names for medications, which could result in medication errors in prescribing, dispensing and consumption. These regulatory authorities may also object to a proposed product name if they believe the name inappropriately makes or implies a therapeutic claim. If the FDA or other regulatory authorities outside the United States object to any of our proposed product names, we may be required to adopt alternative names for our product or product candidates. If we adopt alternative names, either because of our inability to obtain a trademark registration or because of objections from regulatory authorities, we would lose the benefit of our existing trademark applications and the rights attached thereto. Consequently, we may be required to expend significant additional resources in an effort to adopt a new product name that would be registrable under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to

the FDA and other regulatory authorities, which could cause delays in getting our products to market and substantially increase our costs. Furthermore, in the United States and many other jurisdictions, a trademark registration may be cancelled through cancellation or forfeiture proceedings brought by a third party or from non- use of the trademark in that jurisdiction. We may not be able to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product or our product candidates. ~~Our~~ **106Our** rights to develop and commercialize Upstaza ~~and our other gene therapy product candidates~~ are subject, in part, to the terms and conditions of licenses granted to us by others. We depend upon the intellectual property rights granted to us under licenses from third parties that are important or necessary to the development of Upstaza for the treatment of AADC deficiency ~~and our other gene therapy product candidates~~. In particular, we have in- licensed certain intellectual property rights and know- how from National Taiwan University, or NTU, relevant to Upstaza for the treatment of AADC deficiency. Any termination of these licenses could result in the loss of significant or all rights licensed to us and could harm or prevent our ability to commercialize Upstaza for the treatment of AADC deficiency ~~and our other gene therapy product candidates~~. Each of our existing gene therapy licensing agreements are exclusive but are limited to particular fields, such as AADC deficiency and are subject to certain retained rights. Our current gene therapy license agreements, including our agreement with NTU pursuant to which we have in- licensed certain intellectual property rights and know- how relevant to Upstaza for the treatment of AADC deficiency, impose various obligations, including certain payment obligations, including contingent payments to be made upon reaching certain development and regulatory milestones. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to ~~114such~~ **such** agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements, including with respect to Upstaza for the treatment of AADC deficiency, may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business and our ability to realize the anticipated benefits of our acquisition of Agilis. If we cannot maintain a necessary license agreement, including with respect to Upstaza for the treatment of AADC deficiency, or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected product candidates. If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business. We are a party to a number of license agreements and expect to enter into additional licenses in the future. Our existing licenses impose, and we expect that future licenses will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license, in which event we might not be able to market any product that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under such license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms or cause us to lose rights in important intellectual property or technology. We have also received grant funding for some of our development programs from philanthropic organizations and patient advocacy groups pursuant to agreements that impose development and commercialization diligence obligations on us. If we fail to comply with these obligations, the applicable organization could require us to grant to the organization exclusive rights under certain of our intellectual property, which could materially adversely affect the value to us of product candidates covered by that intellectual property even if we are entitled to a share of any consideration received by such organization in connection with any subsequent development or commercialization of the product candidates. Some of our patented technology was developed with U. S. federal government funding. When new technologies are developed with U. S. government funding, the government obtains certain rights in any resulting patents, including a nonexclusive license authorizing the government to use the invention for non- commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise " march- in " rights to use or allow third parties to use our patented technology. The government can exercise its march- in rights if it determines that action is necessary because we fail to achieve practical application of the U. S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U. S. industry. In addition, U. S. government- funded inventions must be reported to the government and U. S. government funding must be disclosed in any resulting patent applications. Furthermore, our rights in such inventions are subject to government license rights and certain restrictions on manufacturing products outside the United States. ~~Risks~~ **107Risks** Related to our Common StockServicing the 2026 Convertible Notes requires a significant amount of cash. We may not have sufficient cash flow from our business to make payments on our debt, and we may not have the ability to raise the funds necessary to settle conversions of, or to repurchase, the 2026 Convertible Notes upon a fundamental change, which could adversely affect our business, financial condition and results of operations. In September 2019, we incurred indebtedness in the amount of $ 287. 5 million in aggregate principal with additional accrued interest under the 2026 Convertible Notes, for which interest is payable semi- annually in arrears on March 15 and September 15 of each year, beginning on March 15, 2020. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance the 2026 Convertible Notes depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt, including the 2026 Convertible Notes. If we are unable to generate cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity capital on terms that may be unfavorable to us or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at the time we seek to refinance such indebtedness. We may ~~115not~~ **not** be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations. Upon conversion of the 2026 Convertible Notes, unless we elect to deliver solely shares of our common stock to settle such conversion (other than paying cash in lieu of delivering any fractional shares), we will be required to make cash payments in respect of the 2026 Convertible Notes being converted. However, we may not have

enough available cash or be able to obtain financing at the time we are required to repurchase 2026 Convertible Notes, to pay the 2026 Convertible Notes at maturity or to pay cash upon conversions of 2026 Convertible Notes. In addition, our ability to repurchase 2026 Convertible Notes or to pay cash upon conversions of 2026 Convertible Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase 2026 Convertible Notes at a time when the repurchase is required by the indenture, to make interest payments on the 2026 Convertible Notes when due under the indenture or to pay any cash payable on future conversions of the 2026 Convertible Notes as required by the indenture would constitute a default under ~~each~~ **the** indenture governing the 2026 Convertible Notes ~~and the Blackstone Credit Agreement~~ . An event of default under the ~~applicable~~ indenture governing the 2026 Convertible Notes or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. If the repayment of any such related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness, repurchase the 2026 Convertible Notes, make interest payments on the 2026 Convertible Notes or make cash payments upon conversions of the 2026 Convertible Notes. Even if holders of the 2026 Convertible Notes do not elect to convert their 2026 Convertible Notes, we could be required to reclassify all of the outstanding principal of the 2026 Convertible Notes as a current rather than long- term liability in accordance with applicable accounting rules, which would result in a material reduction of our net working capital. Any of these factors could materially and adversely affect our business, financial condition and results of operations. 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 corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions 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 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: ● provide for a classified board of directors such that not all members of the board are elected at one time; ● allow the authorized number of our directors to be changed only by resolution of our board of directors; **108** ● limit the manner in which stockholders can remove directors from the board; ● establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors; ● require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent; ● limit who may call stockholder meetings; ● authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a " poison pill " that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and ● require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. ~~116The~~ **The** price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock and lawsuits against us and our officers and directors. Our stock price has been and will likely continue to be volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. The market price for our common stock may be influenced by many factors, including: ● **our ability to maintain our marketing authorization for Translarna for the treatment of nmDMD in the EEA following the CHMP' s negative opinion on the conditional marketing authorization following a re- examination procedure or identify other potential mechanisms in which we may provide Translarna to nmDMD patients in the EEA; ● our ability to maintain the marketing authorization for Translarna and our other products in territories outside of the EEA; ●** expectations with respect to ~~our gene therapy platform~~ **sepiapterin for the treatment of PKU** , including any potential regulatory submissions and potential approvals **; ● expectations with respect to Upstaza** , including ~~those related to Upstaza~~ **any potential regulatory submissions and potential approvals** ; ● any developments related to our ability or inability to execute our commercialization strategy for any of our products; ● our ability to resolve the matters set forth in the FDA' s denial of our appeal to the Complete Response Letter we received from the FDA in connection with our NDA for Translarna for the treatment of nmDMD, and our ability to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost; ● ~~our ability to maintain our marketing authorization for Translarna for~~ **the commercialization of Evrysdi and the development of the SMA program with Roche and the SMA Foundation; ● results of clinical trials of any** ~~the~~ **other product candidate that we develop** ~~treatment of nmDMD in Brazil, Russia and in the EEA, which is subject to the specific obligation to conduct Study 041 and is also subject to annual review and renewal by the European Commission following reassessment of the benefit- risk balance of the authorization by the EMA~~ ; ● any **additional** ~~developments related to Study 041, including with respect to design, timing and conduct, and developments with respect to any~~ clinical or non- clinical trial required by ~~other~~ regulatory agencies **for our products** ~~, including the FDA for~~ **or** ~~Translarna for the treatment of nmDMD; ● the commercialization of Evrysdi and the development of the SMA program with Roche and the SMA Foundation; ● results of clinical trials of any other~~ product ~~candidate~~ **candidates** ~~that we develop~~ ; ● announcements by us or our competitors of significant acquisitions, licenses, strategic collaborations, joint ventures, collaborations or capital commitments; ● negative publicity around our products or product candidates; ● other developments

concerning our regulatory submissions; ● ~~whether regulators in other territories agree with our interpretation of the results of ACT DMD; ●~~ the success of competitive products or technologies; ● results of clinical trials of product candidates of our competitors, including negative results that investors may associate with our product candidates; ● regulatory or legal developments in the United States and other countries; ● developments or disputes concerning patent applications, issued patents or other proprietary rights; **109** ● our ability to realize the benefits of our acquisitions or other business combinations; ● the recruitment or departure of key personnel; ● the loss of distributors, suppliers or manufacturers; ● the level of expenses related to any of our products, product candidates or clinical development programs; ● actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts; ● variations in our financial results or those of companies that are perceived to be similar to us; ● announcements with respect to litigation; ● changes in the structure of healthcare payment systems; ● market conditions in the pharmaceutical and biotechnology sectors; ● general economic, industry and market conditions, including potentially high inflation **rates and sustained high interest** rates; and ● the other factors described in this " Risk Factors " section. Companies that have experienced volatility in the market price of their stock have frequently been the subject of securities class action and shareholder derivative litigation. For example, in 2018 we settled a securities class action lawsuit initiated against us and certain of our current and former executive officers during 2016, as well as derivative lawsuits brought against us, as a nominal defendant, certain of our current and former executive officers and certain of our current and ~~117former~~ --- **former** directors during 2017. We could be the target of other such litigation in the future. Class action and derivative lawsuits, whether successful or not, could result in substantial costs, damage or settlement awards and a diversion of our management' s resources and attention from running our business, which could materially harm our reputation, financial condition and results of operations. Because we do not anticipate paying any cash dividends on our capital in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the development and growth of our business ~~. The terms of the Blackstone Credit Agreement preclude us from paying dividends, other than permitted dividends set forth in the agreement~~ . In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future. The issuance of additional shares of our common stock or the sale of shares of our common stock by our stockholders could dilute our stockholders' ownership interest in the Company and could significantly reduce the market price of our common stock. Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. We have issued a significant number of equity awards under our equity compensation plans or as inducement grants to new hire employees pursuant to Nasdaq rules. The shares underlying these awards are registered on a Form S- 8 registration statement. As a result, upon vesting these shares can be freely exercised and sold in the public market upon issuance, subject to volume limitations applicable to affiliates. The exercise of options and the subsequent sale of the underlying common stock or the sale of restricted stock upon vesting could cause a decline in our stock price. These sales also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate. Certain of our employees, executive officers and directors have entered or may enter into Rule 10b5- 1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5- 1 plan, a broker executes trades pursuant to parameters established by the employee, director or officer when entering into the plan, without further direction from the employee, officer or director. A Rule 10b5- 1 plan may be amended or terminated in some circumstances. Our employees, executive officers and directors may also buy or sell additional shares outside of a Rule 10b5- 1 plan when they are not in possession of material, nonpublic information. **110** ~~Additionally, certain shares that we issued in connection with our acquisitions or other strategic transactions have not yet been sold and are currently restricted as a result of securities laws. These shares may be freely sold in the public market subject to any requirements and restrictions, including any applicable volume limitations, imposed by Rule 144 under the Securities Act. The sale or resale of these shares in the public market, or the market' s expectation of such sales, may result in an immediate and substantial decline in our stock price. Such a decline will adversely affect our investors and also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate. Sales of substantial amounts of shares of our common stock or other securities by our stockholders or by us, including sales made under the Sales Agreement, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $ 125 million from time to time, through the Sales Agent by any method that is deemed to be an " at the market " offering as defined in Rule 415 (a) (4) promulgated under the Securities Act, or the issuance of shares of our common stock upon conversion of our outstanding 2026 Convertible Notes or any future securities convertible or exchangeable into our common stock or in connection with a strategic transaction or otherwise, could dilute our stockholders, lower the market price of our common stock and impair our ability to raise capital through the sale of equity securities. 118~~