Risk Factors Comparison 2024-02-22 to 2023-02-23 Form: 10-K

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Investing in our common stock involves a high degree of risk. In evaluating us and our business, careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10- K for the year ended December 31, ~~2022~~ **2023** and in other documents that we file with the SEC. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing us. New risk factors can emerge from time to time, and we cannot predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations. Risks Related to Our Business Risks Related to Preclinical and Clinical Development CRISPR / Cas9 genome editing technology ~~is not yet~~ **has only recently been** clinically validated for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics using CRISPR / Cas9 systems are unproven and may never lead to marketable products. If we are unable to develop viable product candidates, achieve regulatory approval for any such product candidate or market and sell any product candidates, we may never achieve profitability. We are focused on developing curative medicines utilizing CRISPR / Cas9 genome editing technology, including in vivo therapies and ex vivo engineered cell therapies. Although there have been significant advances in recent years in the fields of gene therapy and genome editing, in vivo CRISPR- based genome editing technologies are relatively new and their therapeutic utility is largely unproven. Our approach to developing therapies centers on using CRISPR / Cas9 technology to alter, introduce or remove genetic information in vivo to treat various disorders, or to engineer human cells ex vivo to create therapeutic cells that can be introduced into the human body to address the underlying disease. Successful development of products by us will require solving a number of issues, including developing or obtaining technologies to safely deliver a therapeutic agent into target cells within the human body or engineer human cells while outside of the body such that the modified cells can have a therapeutic effect when delivered to the patient, optimizing the efficacy and specificity of such products, and ensuring and demonstrating the therapeutic selectivity, efficacy, potency, purity and safety of such products. There can be no assurance we will be successful in solving any or all of these issues. ~~Indeed~~ **With regards to CRISPR / Cas9- based therapies specifically** , ~~no genome editing~~ **we are in clinical- stage development for NTLA- 2001 and NTLA- 2002 and advancing towards clinical testing for our other** in vivo ~~therapy or genome~~ **and ex vivo product candidates. Although one CRISPR / Cas9** - edited ~~engineered cell~~ **ex vivo** therapy has been **recently** approved in the United States (" U. S. ") ~~,~~ **and** European Union (" EU ") **, no genome editing in vivo therapy has been approved in the U. S., EU** countries or other key jurisdictions ~~. With regards to CRISPR / Cas9- based therapies specifically~~ , ~~we are in the initial phases of clinically testing our in vivo~~ and ~~ex vivo product candidates. Further, we are unaware of any clinical trials validating safety and efficacy that have been completed by any third parties. Accordingly,~~ the potential to successfully obtain approval for any of our CRISPR / Cas9 product candidates remains unproven. Our future success also is highly dependent on the successful development of CRISPR- based genome editing technologies, cellular delivery methods and therapeutic applications for the indications on which we have focused our ongoing research and development efforts. We may decide to alter or abandon these programs as new data become available and we gain experience in developing CRISPR / Cas9- based therapeutics. We cannot be sure that our CRISPR / Cas9 efforts and technologies will yield satisfactory products that are safe and effective, sufficiently pure or potent, manufacturable, scalable or profitable in our selected indications or any other indication we pursue. We cannot guarantee that progress or success in developing any particular CRISPR / Cas9- based therapeutic product will translate to other CRISPR / Cas9- based products. Public perception and related media coverage of potential therapy- related efficacy or safety issues, including adoption of new therapeutics or novel approaches to treatment, as well as ethical concerns related specifically to genome editing and CRISPR / Cas9, may adversely influence the willingness of subjects to participate in clinical trials, or if any therapeutic is approved, of physicians and patients to accept these novel and personalized treatments. Physicians, healthcare providers and third ~~-~~party payors often are slow to adopt new products, technologies and treatment practices, particularly those that may also require additional upfront costs and training. Physicians may not be willing to undergo training to adopt these novel and potentially personalized therapies, may decide the particular therapy is too complex or potentially risky to adopt without appropriate training, and may choose not to administer the therapy. Further, due to health conditions, genetic profile or other reasons, certain patients may not be candidates for the therapies. In addition, responses by federal and state agencies, congressional committees and foreign governments to negative public perception, ethical concerns or financial considerations may result in new legislation, regulations, or medical standards that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be. Based on these and other factors, healthcare providers and payors may decide that the benefits of these new therapies do not or will not outweigh their costs. Clinical development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of any product candidates. All of our ~~lead~~ programs are still in the discovery, preclinical or ~~early~~ clinical stage. Our current and future product candidates will require preclinical and clinical activities and studies, regulatory review and approval in each jurisdiction in which we intend to market the products, substantial investment, establishing manufacturing capabilities, access to sufficient commercial manufacturing capacity and

significant marketing efforts before we can generate any revenue from product sales. Before obtaining marketing approval from regulatory authorities for the sale of a product candidate, we must conduct extensive clinical trials to demonstrate the safety, purity, potency and efficacy of the product in humans. It is impossible to predict when or if any of our programs will prove effective and safe in humans or will receive regulatory approval. Preclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We may be unable to establish clinical endpoints that regulatory authorities consider clinically meaningful, and a clinical trial can fail at any stage. 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 approval of their products. Successful completion of clinical trials is a prerequisite to submitting a Biologics License Application (" BLA ") to the **U. S. Food and Drug Administration (" **FDA **")**, and similar applications to comparable foreign regulatory authorities, for each product candidate and, consequently, the ultimate approval and commercial marketing of any product candidates. We do not know whether any of our clinical trials will begin or be completed on schedule, if at all. In addition, the regulatory requirements for later phase clinical trials, such as pivotal trials, are generally more stringent than earlier phase clinical trials, such as Phase 1 trials. We may not meet the requirements of regulatory authorities, such as the ~~U. S. Food and Drug Administration (" FDA ")~~, for initiating later phase clinical trials for our product candidates, which could delay the development of our product candidates **, including the submission of a BLA or comparable marketing application**. Because these are new therapeutic approaches, discovering, developing, manufacturing and commercializing our product candidates may subject us to a number of challenges or delays in completing our preclinical studies and initiating or completing clinical trials. We also may experience numerous unforeseen events during, or as a result of, any current or future clinical trials that we conduct, which could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including: • challenges in obtaining regulatory authorization or approval to ~~commence~~ **conduct** clinical trials in the U. S. from the FDA through an investigational new drug (" IND ") application or from other regulatory agencies outside the U. S., such as the United Kingdom (" U. K. ") Medicines and Healthcare products Regulatory Agency (" MHRA ") or the European Medicines Agency (" EMA "), through corresponding applications, such as a ~~Clinical~~ **clinical** ~~Trial~~ **trial** ~~Application~~ **application** ~~(" CTA ")~~, a Clinical Trial Notification or a Clinical Trial Exemption, because these agencies have very limited or no experience with the clinical development of CRISPR / Cas9-based **therapeutics, particularly in vivo** therapeutics, which may require additional significant testing or data compared to more traditional therapies or otherwise delay the development of our product candidates; • successfully developing processes for the safe administration of these product candidates, including long- term follow- up for patients who receive treatment with any of our product candidates; • regulators, institutional review boards (" IRBs ") or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial; • inability to reach, or delays in reaching, agreement on acceptable terms with trial sites and contract research organizations (" CROs "); • clinical trials of any product candidates may fail to show safety or efficacy, or could produce negative or inconclusive results, which could result in having to conduct additional preclinical studies or clinical trials or terminating the product development programs; • we may not be able to initiate or complete clinical trials of a product candidate if the required number of subjects is larger than we anticipated, the number of subjects willing to enroll is smaller than required, the pace of enrollment is slower than anticipated, or subjects drop out or fail to return for post- treatment follow- up at a higher rate than we anticipated; • we may need to educate medical personnel, including clinical investigators, and patients regarding the potential benefits and side effect profile of each of our product candidates; • regulatory agencies may require us to amend our INDs or equivalent regulatory filings ~~or~~ **,** modify the design of our clinical trials or perform more extensive or lengthier **preclinical or** clinical testing compared to existing therapeutic modalities, **any of** which may delay the initiation or progression of any of our clinical trials; • **animal models may not exist, or available animal models may be inadequate, for some of the human diseases we choose to pursue in our programs, or the preclinical studies we perform as part of our programs; •** our third ~~-~~party contractors may fail to comply with regulatory requirements or meet their performance obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators; • we may elect to, or regulators, IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks; • the cost of preclinical studies and clinical trials of any product candidates may be greater than we anticipate; • the supply or quality of our product candidates or other materials necessary to conduct preclinical studies and clinical trials of our product candidates may be insufficient or inadequate, or not available in a reasonable timeframe, and any transfer of manufacturing activities may require unforeseen manufacturing or formulation changes; • we may face challenges in sourcing preclinical, clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates, which may include importing or exporting materials between different jurisdictions; • our product candidates may have undesirable side effects or other unexpected characteristics **, such as effects or characteristics resulting from their biodistribution or mechanism of action**, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other gene therapies or genome editing- based therapies that raise safety or efficacy concerns about our product candidates; • the FDA or other regulatory authorities may require us to submit additional data, such as long- term toxicology studies, or impose other requirements, including **submitting preclinical data earlier in clinical development compared to existing therapeutic modalities or** requiring amendments to our regulatory filings, before permitting us to initiate or rely on a clinical trial; • we may face challenges in establishing sales and marketing capabilities in anticipation of, and after obtaining, any regulatory approval to gain market authorization; • the FDA or other regulatory authorities may revise the requirements for authorizing our clinical trials or approving our product

candidates, or their interpretation of the authorization or approval requirements may not be what we anticipate **or require us to adopt a Risk Evaluation and Mitigation Strategy (" REMS ") or similar requirements as a condition of approval** ; and • we may not ultimately obtain regulatory approval for a BLA, or corresponding applications outside the U. S., such as a ~~Marketing~~ **marketing** ~~Authorization~~ **authorization** ~~Application~~ **application** ~~from~~ **in** the U. K. and other similar regulatory authorities, such as the EMA, which may have very limited or no experience with the clinical development of CRISPR / Cas9- based therapeutics ~~. In addition~~ , **particularly** ~~disruptions caused by the COVID- 19 pandemic may increase the likelihood that we encounter such difficulties or delays~~ in **vivo therapeutics** ~~initiating, enrolling, conducting or completing our ongoing and planned clinical trials~~ . We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs of the institutions in which such trials are being conducted, the relevant ethics committee or the FDA or other relevant regulatory authorities, or if the Data Monitoring Committee (" DMC ") for such trial recommends such suspension or termination. Such authorities may impose or recommend such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities, resulting in the imposition of a clinical hold, manufacturing or quality control issues, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also **lead to a delay in submitting a BLA or comparable marketing application or** ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials. Additionally, because our in vivo technology potentially involves genome editing across multiple cell and tissue types, we are subject to many of the challenges and risks that other genome editing therapeutics and gene therapies face, including: • regulatory guidance regarding the requirements governing gene and genome editing therapy products have changed and may continue to change in the future, including, e. g., the ~~draft~~ **finalized** guidance document titled " Human Gene Therapy Products Incorporating Human Genome Editing " that the FDA issued in ~~March~~ **January** ~~2022~~ **2024** ; • to date, only a limited number of products that involve in vivo gene transfer have been approved globally; • improper modulation of a gene sequence, including unintended editing events ~~or ,~~ insertion of a sequence into certain locations in a patient' s chromosome **or other effects related to the biodistribution of our product candidates** , could lead to cancer, other aberrantly functioning cells or other diseases, including death; • transient expression of the Cas9 protein or other genome editing components of our product candidates could lead to patients having an immunological reaction towards those cells, which could be severe or life- threatening; • corrective expression of a missing protein in patients' cells could result in the protein being recognized as foreign, and lead to a sustained immunological reaction against the expressed protein or expressing cells, which could be severe or life- threatening; and • regulatory agencies may require extended follow- up observation periods of patients who receive treatment using genome editing products including, for example, the FDA' s recommended 15- year follow- up observation period for these patients, and we will need to adopt such observation periods for our product candidates if required by the relevant regulatory agency, which could vary by country or region. Further, because our ex vivo product candidates involve editing human cells and then delivering modified cells to patients, we are subject to many of the challenges and risks that engineered cell therapies face. For example, patients treated with engineered cell- based gene therapies may experience an allogeneic response leading to allograft rejection and potential local and systemic toxicities, which could be severe or life- threatening. To date, **most** human clinical trials utilizing either in vivo or ex vivo CRISPR- based therapeutics, including our clinical trials for NTLA- 2001 for transthyretin (" ATTR ") amyloidosis and NTLA- 2002 for hereditary angioedema (" HAE "), are still at ~~an early~~ **a clinical** stage **, with only one ex vivo CRISPR- based therapeutic product approved in December 2023 in the U. S. and EU** . We have ongoing clinical trials in various countries for NTLA- 2001 and NTLA- 2002 for patients with ATTR amyloidosis and HAE, respectively. There is no certainty that the FDA or other similar agencies will continue to apply to all our CRISPR / Cas9 product candidates the same regulatory pathway and requirements it is applying to other in vivo therapies or ex vivo engineered therapeutics. In addition, if any product candidates encounter safety or efficacy problems, development delays, regulatory issues or other problems, our development plans and business could be significantly harmed. **For the reasons described above, among others, regulatory bodies, particularly the FDA, have requested, and may request in the future, additional preclinical studies for genome editing products, such as additional studies related to toxicology, biodistribution or reproductive health, and / or preclinical studies earlier in clinical development compared to other therapeutic modalities. Although the FDA cleared the INDs that we have submitted, it is possible that the FDA may impose requirements that result in a delay of any of our programs, including our submission of a BLA or comparable marketing application, or their regulatory approval. For example, following the March 2023 IND clearance for NTLA- 2002, the FDA requested supplemental preclinical data related to the inclusion of female patients of child- bearing potential. We expect to submit these data in advance of the planned Phase 3 trial, which will complement the clinical data collected from female patients of child- bearing potential dosed in the ongoing Phase 1 / 2 study. We cannot guarantee the timing or outcome of these preclinical studies or whether the FDA may require that additional preclinical studies be conducted before commencement of our Phase 3 trial for NTLA- 2002. If we are unable to complete the required studies satisfactorily, the FDA or other regulatory bodies could require that we exclude certain patient populations from clinical studies, place our clinical studies on hold, or require us to cease further clinical studies or deny approval of such product candidates.** Further, competitors that are developing in vivo or ex vivo products with similar technology may experience problems with their product candidates or programs that could in turn cause us to identify problems with our product candidates and programs **, or cause the FDA or other regulatory bodies to impose additional requirements,** that ~~would~~ **could** ~~potentially~~ **cause us to**

delay or pause development of our product candidates. Any of these occurrences may harm our **ability to identify and develop product candidates, and may harm our** business **, financial condition, results of operations and prospects significantly** . We may experience manufacturing delays or other issues that prevent us from executing the clinical trials for NTLA- 2001, NTLA- 2002 **, NTLA- 3001** or our other product candidates on the timeline we expect. Moreover, we cannot guarantee that the FDA, MHRA, the New Zealand Medicines and Medical Devices Safety Authority ~~(" MEDSAFE ")~~, or other regulatory authorities will not change their requirements in the future or approve amendments to our INDs or equivalent regulatory filings, including for NTLA- 2001, NTLA- 2002 **, NTLA- 3001** or our other product candidates on the timeline we expect. Results, including data from our preclinical and clinical studies, are not necessarily predictive of our other ongoing and future preclinical and clinical studies, and they do not guarantee or indicate the likelihood of approval of any potential product candidate by the FDA or any other regulatory agency. If we cannot replicate positive results from any of our preclinical or clinical activities and studies, we may be unable to successfully develop, obtain regulatory approval for and commercialize any potential product candidate. From time to time, we may disclose interim data from our clinical trials, such as the interim results of our ongoing Phase 1 study of NTLA- 2001 or ~~our ongoing~~ Phase 1 / 2 study of NTLA- 2002 **or planned Phase 1 study of NTLA- 3001** . Interim data from clinical trials that have not been completed are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Consequently, interim data should be viewed with caution until we make the final data and analysis available. In addition, there is a high failure rate, as well as potential substantial and unanticipated delays, for product candidates progressing through preclinical and clinical studies. Even if we are able to successfully complete our ongoing and future preclinical and clinical activities and studies for any potential product candidate, we may not be able to replicate, or may have to engage in significant efforts and resource and time investments to replicate, any positive results from these or any other studies in any of our future preclinical and clinical trials, and they do not guarantee approval of any potential product candidate by the FDA or any other necessary regulatory authorities in a timely manner or at all. For more information regarding these risks, see also the remainder of this risk factor section. Negative public opinion and increased regulatory scrutiny of CRISPR / Cas9 use, genome editing or gene therapy generally may damage public perception of the safety of any product candidates that we develop and adversely affect our ability to conduct our business or obtain regulatory approvals for such product candidates. Gene therapy in general, and genome editing in particular, remain novel technologies, with only a limited number of gene therapy products approved to date in the U. S. and EU. Public perception may be influenced by claims that gene therapy or genome editing, including the use of CRISPR / Cas9, is unsafe or unethical, or carries an undue risk of side effects, such as improper modification of a gene sequence in a patient' s chromosome that could lead to cancer, and gene therapy or genome editing may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of diseases targeted by our product candidates prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are more familiar and for which greater clinical data may be available. In addition, responses by the U. S., state or foreign governments to negative public perception or ethical concerns may result in new legislation or regulations that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. More restrictive statutory regimes, government regulations or negative public opinion could have an adverse effect on our business, financial condition and results of operations and prospects, and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, certain gene therapy trials led to several well- publicized adverse events, including cases of leukemia and death. Serious adverse events, such as these, in our clinical trials, or other clinical trials involving gene therapy or genome editing products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidate. In addition, the use of the technology by third parties in areas that are not being pursued by us, such as for targeting and editing of embryonic cells, could adversely impact public and governmental perceptions regarding the ethics and risks of the CRISPR / Cas9 technology and lead to social or legal changes that could limit our ability to apply the technology to develop human therapies addressing disease. For example, reports of the use of CRISPR / Cas9 in China and Russia to edit embryos in utero have generated **,** and may continue to ~~create~~ **generate,** negative public perception about the use of the technology in humans. Negative public and governmental perception of the technology, or additional governmental regulation of our technologies, could also adversely affect our stock price or our ability to enter into revenue generating collaborations or obtain additional funding from the public markets ~~we may expend our limited resources on programs that do not yield a successful product candidate and fail to capitalize on potential product candidates or diseases that may be more profitable or for which there is a greater likelihood of success.If we fail to develop product candidates,our commercial opportunity,if any,will be limited~~ .We are at ~~a clinical~~ **an early** stage of development and our technology and approach has not yet led,and may never lead,to the approval or commercialization of any of our product candidates,including NTLA- 2001 for ATTR amyloidosis or NTLA- 2002 for HAE,or for other product candidates,including NTLA- **2003 and NTLA-** 3001 for alpha- 1 antitrypsin deficiency **(" AATD ") and NTLA- 6001 for CD30 lymphomas** ,being deemed appropriate for clinical development and ultimately approval by a regulatory agency **.In addition,we are identifying collaboration opportunities to advance development of NTLA- 6001** .Even if we are successful in building our pipeline of product candidates,completing clinical development,establishing the necessary manufacturing processes and capabilities,obtaining regulatory approvals and

commercializing product candidates will require substantial additional funding and are subject to the risks of failure inherent in therapeutic product development.Investment in biopharmaceutical product development involves significant risk that any potential product candidate will fail to demonstrate acceptable safety and efficacy profiles,gain regulatory approval,or become commercially viable.We cannot provide any assurance that we will be able to successfully advance any of our product candidates,including NTLA- 2001,NTLA- 2002,NTLA- **2003,NTLA-** 3001 or **NTLA- 6001** ~~product candidates developed through our collaborations~~ ,through the entire research and development process.Any of our other programs may show promise,yet fail to yield product candidates for clinical development or commercialization for many reasons.For more information regarding these risks,see the above risk factor section entitled " Risks Related to Preclinical and Clinical Development." Even if we obtain regulatory approval of any product candidates,such candidates may not gain market acceptance among physicians,patients,hospitals,third **-** party payors and others in the medical community.The use of the CRISPR / Cas9 system to create genome editing- based therapies is a recent development and may not become broadly accepted by patients,healthcare providers,third **-** party payors and other stakeholders.A variety of factors will influence whether our product candidates are accepted in the market,including,for example:• the clinical indications for which our product candidates are approved;• the potential and perceived advantages of our product candidates over alternative treatments;• the incidence and severity of any side effects,including any unintended deoxyribonucleic acid (" DNA ") changes;• product labeling or product insert requirements of the FDA or other regulatory authorities;• limitations or warnings contained in the labeling approved by the FDA or other regulatory authorities;• the timing of market introduction of our product candidates;• availability or existence of competitive products;• the cost of treatment in relation to alternative treatments;• the amount of upfront costs or training required for healthcare providers to administer our product candidates;• the availability of adequate coverage,reimbursement and pricing by government authorities and other third **-** party payors;• patients' ability to access healthcare providers capable of delivering our product candidates;• patients' willingness and ability to pay out- of- pocket in the absence of coverage and reimbursement by government authorities and other third **-** party payors;• the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;• relative convenience and ease of administration,including as compared to alternative treatments and competitive therapies;• any restrictions on the use of our product candidates together with other medications;• interactions of our product candidates with other medicines patients are taking;• potential adverse events for any products developed,or negative interactions with regulatory agencies,by us or others in the gene therapy and genome editing fields;and • the effectiveness of our sales and marketing efforts and distribution support.Even if our products achieve market acceptance,we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our products,are more cost effective or render our products obsolete.In addition,adverse publicity due to the ethical and social controversies surrounding the therapeutic in vivo use of CRISPR / Cas9,genome edited modified cells,or other therapeutics mediums,such as viral vectors that we may use in our clinical trials may limit market acceptance of our product candidates.If our product candidates are approved but fail to achieve market acceptance among physicians,patients,hospitals,third **-** party payors or others in the medical community,we will not be able to generate significant revenue.Our efforts to educate the **healthcare providers,patients and third- party payors about our products may require significant resources and may never be successful** . Risks Related to Competition We face significant competition in an environment of rapid technological change. The possibility that our competitors may achieve regulatory approval before we do or develop therapies that are more advanced or effective than ours may harm our business and financial condition or our ability to successfully market or commercialize our product candidates. The biotechnology and pharmaceutical industries are extremely competitive in the race to develop new products. While we believe we have significant competitive advantages with our industry- leading expertise in genome editing, clinical development expertise and dominant IP position, we currently face and will continue to face competition for our development programs from companies that use genome editing or gene therapy development platforms and from companies focused on more traditional therapeutic modalities such as small molecules and antibodies. The competition is likely to come from multiple sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions. Many of these competitors may have access to greater capital and resources than us. For any products that we may ultimately commercialize, not only will we compete with any existing therapies and those therapies currently in development, but we will also have to compete with new therapies that may become available in the future. **Specific to our NTLA- 2001 program, we are aware of other companies that are currently commercializing or developing products and therapies used to treat ATTR amyloidosis, including Alnylam Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, BridgeBio Pharma Inc., Ionis Pharmaceuticals, Inc., Metagenomi Technologies, LLC, Novo Nordisk A / S and Pfizer, Inc. Specific to our NTLA- 2002 program, we are aware of other companies that are currently commercializing or developing products used to treat HAE, including ADARx Therapeutics, Inc., Astria Therapeutics Inc., BioCryst Pharmaceuticals Inc., BioMarin Pharmaceuticals Inc., CSL Limited, Ionis Pharmaceuticals, Inc., KalVista Pharmaceuticals, Inc., Pharming Group N. V., Pharvaris N. V. and Takeda Pharmaceutical Company Limited.** Competitors in our efforts to provide **other** genetic therapies to patients can be grouped into at least three sets based on their product discovery platforms: Our platform and product foci are on the development of therapies using CRISPR- based technologies. Genome editing companies focused on CRISPR- based technologies include: Beam Therapeutics Inc., Caribou Biosciences, Inc., CRISPR Therapeutics AG, Editas Medicine, Inc., **Metagenomi Technologies, LLC, Prime Medicine, Inc.,** ToolGen, Inc. and Verve Therapeutics Inc. There are also companies developing therapies using additional genome editing technologies, which include Allogene Therapeutics, Inc., bluebird bio, Inc., Cellectis S. A., Homology Medicines, Inc., Poseida Therapeutics, Inc., Precision Biosciences, Inc., Prime Medicine, Inc. and Sangamo Therapeutics, Inc. We are also aware of companies developing therapies in various areas related to our specific research and development programs. For ex vivo, these companies include Allogene Therapeutics, Inc., Cellectis S. A., CRISPR Therapeutics AG and Precision BioSciences, Inc. For in vivo, these companies include CRISPR Therapeutics AG,

Editas Medicine, Inc., Excision Biotherapeutics, Inc., Locus Biosciences, Inc. and **Metagenomi Technologies, LLC,** Precision Biosciences, Inc. ~~Specific to our NTLA- 2001 program, we are aware of other companies that are currently commercializing or developing products~~ and **Verve** ~~therapies used to treat ATTR amyloidosis, including Pfizer, Inc., Alnylam Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Ionis Pharmaceuticals, Inc., BridgeBio Pharma Inc. and Novo Nordisk A / S. Specific to our NTLA- 2002 program, we are aware of other companies that are currently commercializing or developing products used to treat HAE, including Takeda Pharmaceutical Company Limited, Astria~~ Therapeutics Inc ~~., ADARx Therapeutics, Inc., BioCryst Pharmaceuticals Inc., BioMarin Pharmaceuticals Inc., Pharming Group N. V. and CSL Limited~~ . Our competitors will also include companies that are or will be developing other genome editing methods as well as small molecules, biologics, in vivo gene therapies, engineered cell therapies and nucleic acid- based therapies for the same indications that we are targeting with our CRISPR / Cas9- based therapeutics. Any advances in gene therapy, engineered cell therapies or genome editing technology made by a competitor may be used to develop therapies that could compete against any of our product candidates. Many of these competitors have substantially greater research and development capabilities and financial, scientific, technical, intellectual property, manufacturing, marketing, distribution and other resources than we do, and we may not be able to successfully compete with them. Even if we are successful in selecting and developing any product candidates, in order to compete successfully we may need to be first- to- market or demonstrate that our CRISPR / Cas9- based products are superior to therapies based on the same or different treatment methods. If we are not first- to- market or are unable to demonstrate such superiority, any products for which we are able to obtain approval may not be commercially successful. Furthermore, in certain jurisdictions, if a competitor has orphan drug status for a product and if our product candidate is determined to be contained within the scope of a competitor' s orphan drug exclusivity, then approval of our product for that indication or disease could potentially be blocked, for example, for up to seven years in the U. S. and 10 years in the EU. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease our value and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. Risks Related to ~~Manufacturing~~ **Commercialization If, in the future, we are unable to establish sales, marketing** and ~~Supply In vivo genome editing~~ **distribution capabilities or enter into agreements with third parties to sell, market and distribute** products ~~and ex vivo engineered cell therapies~~ based on **our** ~~CRISPR / Cas9 genome editing technology~~ **technologies , we** ~~are novel and~~ may **not** be **successful** ~~complex and difficult to manufacture. We could experience manufacturing problems that result~~ in ~~delays in the development, approval or commercialization~~ --- **commercializing** ~~of~~ our **products if and when any** product candidates or ~~otherwise harm~~ **therapies are approved and we may not be able to generate any revenue. We do not currently have a sales, marketing** ~~our~~ - **or** ~~business~~ **distribution infrastructure and, as a company, have no experience in the sale, marketing or distribution of therapeutic products** . ~~The manufacturing process used to~~ **To achieve commercial success for any approved** ~~produce~~ **product** ~~CRISPR / Cas9~~ **candidate for which we retain sales and marketing responsibilities, we must build our sales, marketing, managerial and other non** - ~~based in vivo~~ **technical capabilities or make arrangements with third parties to perform these services. There are risks involved with both establishing our own sales** and ~~engineered cell therapy~~ **marketing capabilities and entering into arrangements with third parties to perform these services. Factors that may inhibit our efforts to commercialize our** product candidates **include: •** ~~may be complex, as they are novel and have not been validated for late phase clinical and commercial production and may require components that are difficult to obtain or~~ **our inability to recruit** ~~manufacture at the necessary quantities and in accordance with regulatory requirements. Several factors could cause production interruptions~~ , **train and retain adequate numbers of effective sales and marketing** ~~including equipment malfunctions; facility unavailability or contamination; raw material cost, shortages or contamination; natural disasters, such as the COVID- 19 pandemic; disruption in utility services; human error; insufficient~~ personnel; **• the** inability ~~to meet legal or regulatory requirements; or disruptions in the operations~~ of **sales personnel to obtain access to physicians** ~~our~~ - **or persuade adequate numbers** ~~suppliers. Because our product candidates are regulated as biologics, their processing steps will be more complex than those~~ of ~~most small molecule drugs. Moreover, unlike small molecules, the physical~~ **physicians** ~~and chemical properties of a complex product such as ours generally cannot be fully characterized. As a result, assays of the finished product or relevant components may not be sufficient~~ to **prescribe any future** ~~ensure that the product will perform in the intended manner. For this reason, we will employ multiple steps to control the manufacturing process to ensure that the process results in~~ product candidates that ~~meet~~ **we may develop; •** ~~their~~ -- **the** ~~specifications~~ **lack of complementary treatments to be offered by sales personnel** , ~~but complications~~ **which may put us** at ~~any one step could adversely impact our manufacturing~~ **a competitive disadvantage relative to companies with more extensive product lines; • the location** of **patients in need of our product candidates and the treating physicians who may prescribe the** products **;** ~~. Further, we may encounter problems achieving adequate quantities~~ and **• unforeseen costs and expenses, as well as legal and** ~~quality of clinical grade materials that meet the FDA or other relevant~~ regulatory **requirements, associated** ~~agency' s applicable standards or our specifications~~ with ~~consistent~~ **creating** and ~~acceptable production yields~~ **operating a sales** and ~~costs~~ **marketing organization** . ~~Manufacturing process irregularities~~ **If we enter into arrangements with third parties to perform sales** , **marketing and distribution services** ~~even minor deviations from the normal process~~ , **we** ~~could~~ **would** ~~result in~~ **likely have lower** product ~~defects~~ **revenue or profitability than if we ourselves were to market and sell** ~~or~~ **our** ~~manufacturing issues that cause lot failures,~~ product **candidates** ~~recalls, product liability claims and litigation, insufficient inventory or production interruption~~ . In addition, **we may** ~~product manufacturing and supply could~~ be ~~delayed if the FDA~~ **unable to enter into sales** and ~~other regulatory authorities require~~ **marketing arrangements with third parties, or into arrangements with terms that are favorable to** us ~~to submit lot samples, testing results~~ **. We likely will have little control over such third parties** and **any of** ~~protocols, or if they require that we not distribute a lot until they authorize the~~ **them** ~~product' s release. Further, certain of~~ **may fail to devote the necessary**

resources and attention to sell and market our product candidates **effectively. If we do not establish** ~~may require components that are unavailable or difficult to acquire or manufacture at the necessary scale~~ **sales** ~~and in compliance with regulatory requirements to support our clinical trials or~~ , ~~if approved~~ **marketing and distribution capabilities successfully** , **either** ~~commercial efforts. We expect to continue to rely~~ on ~~third- party contract manufacturing organizations (" CMOs ") to manufacture these components and the final product candidates for the foreseeable future. We may not have full control of these CMOs and they may prioritize other customers or~~ **our** ~~be unable to provide us with enough manufacturing capacity to meet our objectives. Further, we may rely on~~ **own** ~~CMOs outside the U. S. for~~ **or through** certain components of our product candidates,..... clinical studies or those of any other third parties, ~~including with respect to genome editing technology or engineered cell therapies, are inconclusive or fail to show efficacy or if such clinical trials give rise to safety concerns or adverse events,~~ we may: • be prevented from,..... biopharmaceutical products is inherently risky. We may not be successful in **commercializing** our ~~efforts~~ **product candidates, and our business, results of operations, financial condition and prospects will be materially adversely affected. Risks Related** to **Employee Matters** ~~or disrupt the execution of our business~~ and ~~operational plans.~~ **Managing Our Workforce** Our future success depends on our ability to retain key executives and to attract,retain and motivate qualified personnel.We are highly dependent on the research and development,clinical, **manufacturing,commercialization,** legal,financial and business development expertise of John M.Leonard,M.D.,our President and Chief Executive Officer, **James Basta,our Executive Vice President,General Counsel and Corporate Secretary,Eliana Clark,our Executive Vice President and Chief Technical Officer,** Glenn Goddard,our Executive Vice President,Chief Financial Officer and Treasurer, **Derek Hicks,our Executive Vice President and Chief Business Officer,** David Lebwohl,our Executive Vice President and Chief Medical Officer, ~~James Basta,our Executive Vice President,General Counsel~~ and ~~Corporate Secretary,~~ Laura Sepp- Lorenzino,our Executive Vice President and Chief Scientific ~~Officer,Eliana Clark,our Executive Vice President and Chief Technical Officer and Derek Hicks,our Executive Vice President and Chief Business~~ Officer,as well as the other principal members of our management,scientific and clinical teams.Although we have entered into employment arrangements with our executive officers,each of them may terminate their employment with ~~use~~ **us** ~~and enhance~~ **at any time. We do not maintain " key person " insurance for any of our executives** ~~our~~ ~~our management,scientific and clinical teams.Although we have entered into employment arrangements with our executive officers,each of them may terminate their employment with us at any time.We do not maintain " key person " insurance for any of our executives~~ or other employees **.Execution of our business plans and strategies requires capable personnel with specialized skills and expertise in the research,development,manufacturing and commercialization of biopharmaceutical products,and,as a result,we may encounter difficulties in hiring or retaining capable personnel in key positions** .Recruiting and retaining qualified scientific,clinical,manufacturing and sales and marketing personnel will also be important for our success.The loss of the services of our executive officers or other key employees could impede the achievement of our research,development and commercialization objectives,and seriously harm our ability to successfully implement our business strategy.Furthermore,replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop,gain regulatory approval of and commercialize products using our technology.Competition to hire from this limited pool is intense,and we may be unable to hire,train,retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies,universities and research institutions for similar personnel.The market for qualified personnel in the biotechnology space generally,and ~~genome~~ genome editing ~~technology to create a pipeline of product candidates, establish the necessary manufacturing capabilities, obtain regulatory approval~~ and ~~develop commercially successful products~~ **gene therapy fields in particular** , ~~or~~ **in and around the Cambridge, Massachusetts area is especially competitive. In addition,** we **rely** ~~may expend our limited resources~~ on ~~programs~~ **consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategies. 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 ~~do~~ **may limit their availability to us. Further, some of the qualified personnel that we hire and recruit are** not ~~yield a successful product candidate~~ **U. S. citizens,** and ~~fail to capitalize on potential product candidates or diseases that may be more profitable or for which~~ there is ~~a greater likelihood~~ **uncertainty with regard to their future employment status due to the current U. S. administration' s announced intention** of ~~success~~ **modifying the legal framework for non- U. S. citizens to be employed in the U. S** . If we ~~fail~~ **are unable** to ~~develop product candidates~~ **continue to attract and retain high quality personnel** , our ~~commercial opportunity, if any,~~ **ability to pursue our growth strategy** will be limited . We are at an early stage..... significant resources and may never be successful . Risks Related to Healthcare Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell any product candidates or therapies profitably. The success of our product candidates, if approved, depends on the availability of adequate coverage and reimbursement from third ~~-~~party payors, including government agencies, private health insurers and health maintenance organizations. There is significant uncertainty related to the insurance coverage and reimbursement of any newly approved product, but in particular novel genome editing and engineered cell products. All the therapeutic indications approved by the relevant authorities may not be covered or reimbursed. In addition, we cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates because they are novel treatments for diseases using a new technology and delivery approaches. For more information on coverage and reimbursement ~~please~~ see the section entitled " Business – Government Regulation and Product Approval – Coverage and Reimbursement. " In the U. S. and some other jurisdictions, patients generally rely on third ~~-~~party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid in the U. S., and commercial payors are critical to new product acceptance. Government authorities and other third ~~-~~party payors, such as private health insurers and

health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. In the U. S., the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services (" CMS "), an agency within the U. S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare, and private payors often follow CMS' s coverage decisions. Other jurisdictions have agencies, such as the National Institute for Health and Care Excellence in the U. K., that evaluate the use and cost- effectiveness of therapies, which impact the utilization and price of the medicine in such jurisdiction. In the U. S., no uniform policy of coverage and reimbursement for products exists among third ~~-~~party payors. As a result, obtaining coverage and reimbursement approval of a product from a third ~~-~~party payor is a time- consuming and costly process that could require us to provide supporting scientific, clinical and cost- effectiveness data for the use of our products to each potential payor, with no assurance that coverage and adequate reimbursement will be obtained from all or any of them. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might be insufficient or may require co- payments that patients find unacceptably high, which may prevent us from achieving or sustaining profitability. Additionally, third ~~-~~party payors may not cover, or provide adequate reimbursement for, long- term follow- up evaluations required following the use of our genome editing products. In addition, each country in which we seek approval to market our product candidates has unique laws and market practices regulating coverage and reimbursement for human therapeutics. Market acceptance and sales of our products in each country will depend on our ability to meet each of these jurisdiction' s requirements for coverage and reimbursement. Further, changes to the country' s existing requirements may also affect our ability to commercialize our products in the future, or achieve profitability from their sale. We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws, health information privacy and security laws and anti- corruption laws. If we are unable to comply, or have not fully complied, with such laws or their relevant foreign counterparts, we could face substantial penalties. The sale, distribution and marketing of human therapeutics and our relationship with healthcare providers are strictly regulated by laws in the U. S. and most other jurisdictions in which we intend to seek approval for our product candidates. In addition, the collection and use of ~~Personally Identifiable Information~~ **personal information** , including Protected Health Information (" PHI "), is regulated by federal, state and foreign privacy, data security and data protection laws. Failure to comply with these laws could impair our ability to properly sell our product candidates in particular jurisdictions and subject us to liability from private and governmental entities. Addressing these diverse and sometimes contradictory requirements in myriad jurisdictions may necessitate that we expend significant resources on compliance efforts. Any failure to comply with these requirements may leave us exposed to possible enforcement actions and potential liability. For more information on these laws and regulations ~~please~~ see the section titled " Business – Government Regulation and Product Approval – Other Healthcare and Privacy Laws. " The scope and enforcement of each of these laws is not always certain and is subject to legislative, judicial or prosecutorial changes. Further, because of the breadth of these laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Indeed, U. S. federal and state enforcement bodies have increasingly scrutinized healthcare companies and providers interactions, which has led to a number of investigations, prosecutions, convictions and settlements in the industry. Ensuring business arrangements comply with applicable laws, as well as responding to possible investigations by government authorities, can be time- and resource- consuming and can divert **the** ~~a company' s~~ attention **of our staff and resources** from ~~its~~ **performing the duties required for the general operation of our** business. The increasingly global nature of our business operations, including clinical development efforts, subjects us to domestic and foreign anti- bribery and anti- corruption laws and regulations, such as the Foreign Corrupt Practices Act (" FCPA ") and the U. K. Bribery Act. These activities create the risk of unauthorized payments or offers of payments that are prohibited under the FCPA, the U. K. Bribery Act or similar laws. It is our policy to implement safeguards to discourage these practices by our employees and agents. However, these safeguards may ultimately prove ineffective, and our employees, consultants, and agents may engage in conduct for which we might be held responsible. Violations of the FCPA may result in severe criminal or civil sanctions, and we may be subject to other liabilities, which could negatively affect our business, operating results and financial condition. Further, the U. S. federal and state ~~government~~ **governments** , as well as other jurisdictions, have myriad laws regulating the collection, storage, distribution **, safeguarding** and use of ~~data~~ **personal information** of employees, patients, agents, and others. These different laws governing the privacy and security of health and other personal information often differ from each other in significant ways and may not have the same effective requirements, thus complicating efforts to comply with their respective provisions. For example: • in the U. S., ~~the Health Insurance Portability and Accountability Act of 1996 (" HIPAA ")~~ , as amended by ~~the Health Information Technology for Economic and Clinical Health Act of 2009 (" HITECH ")~~ , imposes requirements relating to the privacy, security and transmission of PHI on certain covered healthcare providers, health plans, and healthcare clearinghouses, and their respective business associates that perform services for them that involve the use or disclosure of such information. These laws impose civil and criminal monetary penalties, and give state attorneys general the authority to file civil actions for damages or injunctions, and attorney' s fees, in federal courts to enforce the laws; • the California Consumer Privacy Act (" CCPA ") requires covered companies to provide ~~new~~ disclosures to California consumers and afford such consumers ~~new~~ rights with respect to their personal information, including the rights to: request deletion of their information, receive the information on record for them, know what categories of information are being maintained about them, and opt- out of certain sales of their information. The CCPA provides for civil penalties for violations, as well as a private right of action for certain data breaches that result in the loss of personal information, which may increase the likelihood of, and risks associated with, data breach litigation. The CCPA **was amended by** ~~became effective in January 2020 and enforceable in July 2020; • further, a new California privacy law,~~ the California Privacy Rights Act (" CPRA ") **, which became effective** ~~was passed by California voters~~ on ~~November 3, 2020 and entered into force~~ January 1, 2023. The CPRA substantially ~~modifies~~ **modified** the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information ~~and~~ **,** by establishing a state agency vested

with the authority to enforce the CCPA **and by creating** ~~. The CPRA also creates~~ additional obligations with respect to the processing of personal information, including regulating personal information collected about employees, applicants and retirees as well as that which is collected in a business to business capacity. We anticipate additional costs associated with CCPA **and other U. S. state privacy law** compliance and we cannot yet fully determine the impact that **such** ~~the CCPA or other privacy~~ laws, regulations and standards may have on our business; • **broad consumer privacy and data protection laws have been or are predicted to be passed in a number of additional states. Many state privacy and data protection laws differ from each other in significant ways, and it is not yet fully clear how these laws will be enforced and interpreted. In addition, other states have passed laws regulating specific aspects of privacy. For example, the State of Washington recently passed a law that regulates health and medical information that is not subject to HIPAA and a small number of states have enacted laws that specifically target the collection and use of biometric information. Furthermore,** other U. S. states ~~, such as Massachusetts, Nevada, Illinois, Pennsylvania, Ohio, North Carolina, New Jersey and New York,~~ have enacted ~~and / or are considering laws that impose~~ stringent ~~privacy and / or~~ data security ~~requirements and, most notably, stringent new privacy~~ laws ~~will become effective in Colorado, Virginia, Utah, Connecticut and California in 2023~~ ; and • around the world, many countries have enacted laws that regulate data protection. In the EU and ~~European Economic Area (“~~ EEA ~~”)~~ the collection and use of personal data is regulated by the General Data Protection Regulation ~~(“ GDPR ”)~~ and the member states' related data protection and privacy laws, and in the U. K. by ~~its Data Protection Act 2018 and, as of January 1, 2021,~~ the U. K. GDPR ~~(such laws collectively being described as “ European Data Protection Law ”)~~ . Because the European Data Protection Law applies not only to businesses that are established within the ~~EU~~ **EEA or the U. K.** but also to any business that offers goods or services to individuals in ~~the~~ **those territories** ~~EU or U. K.~~ , it could apply to us. European Data Protection Law imposes strict requirements, including special protections for “ sensitive ” personal data which includes health and genetic information of individuals in the ~~EU~~ **EEA** or the U. K.; expanded disclosures about the personal data use; information retention limitations; mandatory data breach notification requirements; and additional oversight obligations relating to third parties retained to process the personal data. European Data Protection Law grants or enhances the rights of individuals with respect to their personal data, including the rights to object to the processing of the data and request deletion of the same. ~~It also has~~ **In addition, European Data Protection Laws include** strict requirements on **, and prohibit,** the transfer of personal data **subject to European Data Protection Law** ~~out of the EU or the U. K.~~ to jurisdictions that have not been deemed **by competent authorities** to offer “ adequate ” privacy protections **(“ third countries ”)** , **unless a derogation exists or a valid** ~~such as the U. S. Failure to comply with the requirements of the~~ European Data Protection Law **transfer mechanism (for example, the EC approved Standard Contractual Clauses, certification to the EU- U. S. Data Privacy Framework (which allows for transfers for relevant U. S.- based organizations who self- certify compliance and participate in the framework) and the U. K. International Data Transfer Agreement / Addendum) has been put in place and a transfer impact assessment has been carried out. Our compliance with international data transfer obligations under European Data Protection Law, where applicable, may require significant effort and cost, and may limit our ability to transfer such personal data to other jurisdictions or to work with certain service providers that process personal data, and may require us to make strategic considerations around where such personal data is stored. Further, although the EC has acknowledged that the U. K. currently has adequate protections for international data transfers, there may be post- Brexit developments in the future that result in additional costs and operational challenges in complying with the U. K. GDPR and any other developments regulating the transfer of personal data between the U. K. and EU. For example, the U. K. government has now introduced a Data Protection and Digital Information Bill (the “ U. K. Bill ”) into the U. K. legislative process. The aim of the U. K. Bill is to reform the U. K.' s data protection regime following Brexit. If passed, the final version of the U. K. Bill may have the effect of further altering the similarities between the U. K. and EEA data protection regime and threaten the U. K. adequacy decision from the EC. Failure to comply with the requirements of the European Data Protection Law** may result in warning letters, mandatory audits, orders to cease / change the use of data, and financial penalties, including fines of up to 4 % of global revenues, or 20 **. 0 million** ~~, 000, 000 Euro~~ **Euros** (£ 17. 5 million in the U. K.), whichever is greater. Moreover, data subjects can seek damages for violations, and non- profit organizations can bring claims on behalf of data subjects. The costs associated with ensuring compliance with these laws, including in particular European Data Protection Law, may be onerous and **may** adversely affect our business, financial condition, results of operations and prospects ~~. Further, due to Brexit, we may have additional costs and operational challenges in complying with the U. K. GDPR and any other developments regulating the transfer of personal data between the U. K. and EU~~ . We may also need to rely on multiple third parties **, such as partners and service providers,** to meet these legal requirements, which could result in additional liability for us if they do not comply. Efforts to ensure that we comply with all applicable healthcare and data privacy laws and regulations, as well as other domestic and foreign legal requirements, will involve substantial costs. It is possible that governmental and enforcement authorities in the U. S. or outside the U. S. will conclude that our business practices do not comply with current or future legal requirements. If any noncompliance actions are instituted against us, ~~and we are not successful in defending ourselves or asserting our rights,~~ those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, disgorgement, monetary fines, individual imprisonment, exclusion from participation in federal healthcare programs (such as Medicare and Medicaid), contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, any of which could adversely affect our ability to operate our business and ~~our~~ **affect the** results of **our** operations. Any action ~~for~~ **alleging a** violation of these laws, even if successfully defended, could result in significant legal expenses and divert management' s attention from the operation of the business. Prohibitions or restrictions on sales (including importation or exportation) or withdrawal of future marketed products could materially affect business in an

adverse way. Healthcare cost control initiatives, including healthcare legislative and regulatory reform measures, may have a material adverse effect on our business and results of operations. The U. S. and many other jurisdictions have enacted or proposed legal changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates, affect our ability to profitably sell our product candidates once approved, and restrict or regulate post- approval activities. Changes in the legal requirements, or their interpretation, could impact our business by compelling, for example, modification to: our manufacturing arrangements; product labeling; pricing and reimbursement arrangements; private or governmental insurance coverage; the sale practices for, or availability of, our products; or record- keeping activities. If any such changes were to be imposed, they could adversely affect the operation of our business. For more information on these laws and regulations ~~please~~ see the section entitled " Business – Government Regulation and Product Approval – Healthcare Reform. " Third ~~-~~party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In the U. S. and certain other jurisdictions, there have been, and are expected to continue to be, a number of legislative and regulatory changes to the healthcare system that could impact our ability to sell our products profitably. In the U. S., however, significant uncertainty exists regarding the provision and financing of healthcare because the newly elected administration and federal legislators have publicly declared their intention to review and potentially significantly modify the current legal and regulatory framework for the healthcare system **. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and / or impose price controls may adversely affect: • the demand for our product candidates, if we obtain regulatory approval; • our ability to set a price that we believe is fair for our approved products; • our ability to generate revenue and achieve or maintain profitability; • the level of taxes that we are required to pay; and • the availability of capital** . Current legislation at the U. S. federal and state levels seeks to reduce healthcare costs and improve the quality of healthcare. For example, the U. S. Affordable Care Act (" ACA "), enacted in March 2010, subjected biologic products to potential competition by lower- cost biosimilars; introduced a new methodology to calculate manufacturers' rebates under the Medicaid Drug Rebate Program for certain drugs, including infused or injected drugs; increased manufacturers' minimum Medicaid rebates under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate Program to pharmaceutical prescriptions of individuals enrolled in Medicaid managed care organizations; imposed new annual fees and taxes for certain branded prescription drugs and biologic agents; created the Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70 % point- of-sale discounts as of January 1, 2019, off negotiated prices on certain brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer' s outpatient drugs to be covered under Medicare Part D; and provided incentives to programs that increase the federal government' s comparative effectiveness research. Congress also could consider additional legislation to repeal, replace, or further modify elements of the ACA. Thus, the full impact of the ACA, or any law replacing elements of it, and the political uncertainty regarding any repeal and replacement on the ACA, on our business remains unclear. There have been, and likely will..... distraction to our management and employees. Risks Related to Our Common Stock Risks Related to Investment in Securities An active trading market for our common stock may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at or above the prices at which they acquired their shares or sell their shares at the time they would like to sell. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration. The price of our common stock historically has been volatile, which may affect the price at which you could sell any shares of our common stock. The market price for our common stock historically has been highly volatile and could continue to be subject to wide fluctuations in response to various factors. This volatility may affect the price at which you could sell the shares of our common stock, and the sale of substantial amounts of our common stock could adversely affect the price of our common stock. Our stock price is likely to continue to be volatile and subject to significant price and volume fluctuations in response to market and other factors, including: • the success of our products or technologies or competing products or technologies; • results of clinical trials of our product candidates or those of our competitors; • developments or disputes concerning issued patents, patent applications or other intellectual property rights; • regulatory or legal developments in the U. S. and other countries; • the recruitment or departure of key personnel; • the level of expenses related to any of our product candidates or clinical development programs; • the results of our efforts to discover, develop, manufacture, acquire or in- license our current and additional product candidates or products; • actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts; • variations in our financial results or the financial results of companies that are perceived to be similar to us; • sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares; • changes in the structure of healthcare payment systems; • market conditions in the pharmaceutical and biotechnology sectors; • public perception of the safety of genome editing based therapeutics; • general economic, industry and market conditions; and • the other factors summarized and described in this Risk Factors section ~~. In addition, the COVID- 19 pandemic affected the volatility of the trading prices for our common stock and other biopharmaceutical companies. The extent to which the outbreak may impact our business, preclinical studies and ongoing and planned clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the emergence of new variants of the disease, the ability of governments to vaccinate their populations and that existing vaccines can treat any new variants effectively, the ultimate containment of the disease, the modification or lifting of travel restrictions and other actions implemented to contain the outbreak or address its impact, such as social distancing and quarantines or lock- downs in the U. S. and other countries, business closures or business disruptions, and the ultimate effectiveness of other actions taken in the U. S. and other countries to contain and address the disease. A resurgence or other negative developments relating to the pandemic~~

~~may require us to again restrict access to our offices and laboratories, or to pause or suspend preclinical research and our clinical trial; and, further, may disrupt our manufacturing and supply chain or those of our third- party suppliers and manufacturers~~ . Companies trading in the stock market in general, and in The Nasdaq Global Market in particular, have also experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. In the past, following periods of volatility in the market, securities class- action litigation has often been instituted against companies. Such litigation, if instituted against us, could result in substantial costs and diversion of management' s attention and resources, which could materially and adversely affect our business, financial condition, results of operations and growth prospects. If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, our stock price and trading volume could decline. The trading market for our common stock will depend, in part, on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts may not publish an adequate amount of research on us, which may negatively impact the trading price for our stock. In addition, if one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline. Further, if our operating results fail to meet the forecasts of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline. Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Risk Related to Ownership Generally Our principal stockholders and management own a significant percentage of our stock and, if they choose to act together, will be able to control or exercise significant influence over matters subject to stockholder approval. As of December 31, ~~2022~~ **2023** , our executive officers, directors, 5 % or greater stockholders and their affiliates beneficially owned approximately ~~30~~ **38** . ~~5~~ **4** % of our outstanding voting stock. These stockholders may have the ability to influence us through their ownership positions. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders. We have broad discretion over the use of our cash, cash equivalents and marketable securities, and may not use them effectively **, including that we may be exposed to liquidity issues and other systemic financial risks at the financial institutions holding our cash and cash equivalents** . Our management has broad discretion to use our cash, cash equivalents and marketable securities to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending our use to fund operations, we may invest our cash, cash equivalents and marketable securities in a manner that does not produce income or that loses value **. A portion of our cash may be held by financial institutions that may have been, or could in the future become, exposed to liquidity issues, bank failures or other systemic financial risks. Our uninsured cash deposits with such financial institutions may be at risk in the event they experience liquidity problems or other financial losses. For example, in May 2023, the Federal Deposit Insurance Corporation (" FDIC ") took control of First Republic Bank and JP Morgan Chase & Co. has since acquired a substantial amount of assets and certain liabilities of First Republic. Although the U. S. Department of Treasury, FDIC and Federal Reserve Board have announced a program to provide up to $ 25. 0 billion of loans to financial institutions secured by certain government securities held by financial institutions to mitigate the risk of potential losses on the sale of such instruments, there is no guarantee that such loans will fully mitigate the risk of potential losses or that the U. S. Department of Treasury, FDIC and Federal Reserve Board will provide access to uninsured funds in the future in the event of the closure of other banks or financial institutions, or that they would do so in a timely fashion. We assess our banking relationships as we believe necessary or appropriate, but uncertainty remains over liquidity concerns in the broader financial services industry, and our business, our business partners, or industry as a whole may be adversely impacted in ways that we cannot predict at this time, including our ability to access cash in amounts adequate to finance or capitalize our current and / or projected business operations could be significantly impaired by factors that affect the financial institutions with which we have banking relationships, and in turn, us. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements (including cash management arrangements), disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry. In addition, our vendors, such as our CMOs, CROs or business partners, may be susceptible to the foregoing liquidity or other financial risks and factors, which could, in turn, have a material adverse effect on our current and / or projected business operations and results of operations and financial condition** . We incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices. As a public company, and particularly since we are no longer an " emerging growth company " under applicable SEC regulations, we incur significant legal, accounting and other expenses. The Sarbanes- Oxley Act of 2002, the Dodd- Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance

practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Pursuant to Section 404 of the Sarbanes- Oxley Act of 2002 (" Section 404 "), we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. We conduct a process each year to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we dedicate internal resources, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements. Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of stockholders and could cause our stock price to fall. We will need additional capital in the future to continue our planned operations in addition to the proceeds we received from our initial public offering (" IPO ") in May 2016 and follow- on public offerings **since then** ~~in November 2017, June 2020, December 2020, and July 2021~~ . To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders. ~~On August 23~~ **In March 2022** , ~~2019,~~ we ~~filed a Registration Statement on Form S- 3, as amended (the " 2019 Shelf ") with the SEC, which was declared effective on September 12, 2019 (File No. 333- 233448) in relation to the registration of common stock, preferred stock, debt securities, warrants and units of any combination thereof. We also simultaneously~~ entered into an Open Market Sale Agreement (the " ~~2019~~ **2022** Sale Agreement ") with **Jefferies LLC (** the **")** , to provide for the offering, issuance and sale of up to an aggregate amount of $ ~~150~~ **400** . 0 million of our common stock from time to time in " at- the- market " offerings ~~under the 2019 Shelf and subject to the limitations thereof~~ . We ~~paid~~ **will pay** to the Sales Agent cash commissions of 3. 0 % of the gross proceeds of sales of common stock under the ~~2019~~ **2022** Sale Agreement. Through December 31, ~~2022~~ **2023** , we issued ~~3~~ **7** , ~~778~~ **518** , ~~889~~ **163** shares of our common stock at an average price of $ ~~37. 80 per share in accordance with the 2019 Sale Agreement for aggregate net proceeds of $ 138. 0 million, after payment of cash commissions to the Sales Agent and approximately $ 0. 5 million related to legal, accounting and other fees in connection with the sales. As of September 30, 2022, the 2019 Sale Agreement had expired. In June 2020, we issued 6, 301, 370 shares of our common stock, including the exercise in full by the underwriters of their option to purchase an additional 821, 917 shares, at the public offering price of $ 18. 25 per share pursuant to the 2019 Shelf for aggregate cash consideration of $ 107. 7 million, after payment of commissions and fees and approximately $ 0. 4 million related to legal, accounting and other fees in connection with the sales. In June 2020 we also issued 925, 218 shares of our common stock to Regeneron in a private placement for an aggregate cash consideration of $ 30. 0 million, or $ 32.~~ 42 ~~per share, representing a 100 % premium over the volume- weighted average trading price of the Company' s common stock during the 30- day period prior to the closing~~ . **70** ~~On November 30, 2020, we filed a Registration Statement on Form S- 3ASR (the " Universal Shelf ") with the SEC, which was automatically declared effective upon filing (File No. 333- 251022) in relation to the registration of common stock, preferred stock, debt securities, warrants and units of any combination thereof. In December 2020, we issued 5, 513, 699 shares of our common stock, including the exercise in full by the underwriters of their option to purchase an additional 719, 178 shares, at the public offering price of $ 36. 50 per share pursuant to the Universal Shelf for aggregate cash consideration of $ 188. 9 million, after deducting the underwriting discount, commissions and offering expenses. In July 2021, we issued 4, 758, 620 shares of our common stock, including the exercise in full by the underwriters of their option to purchase an additional 620, 689 shares, at the public offering price of $ 145. 00 per share pursuant to the Universal Shelf for aggregate cash consideration of approximately $ 648. 3 million, after deducting the underwriting discount, commissions and estimated offering expenses. In March 2022, we entered into an Open Market Sale Agreement (the " 2022 Sale Agreement ") with the Sales Agent, to provide for the offering, issuance and sale of up to an aggregate amount of $ 400. 0 million of our common stock from time to time in " at- the- market " offerings under the Universal Shelf and subject to the limitations thereof. We will pay to the Sales Agent cash commissions of 3. 0 % of the gross proceeds of sales of common stock under the 2022 Sale Agreement. Through December 31, 2022, we issued 3, 395, 339 shares of our common stock at an average price of $ 57. 43~~ per share in accordance with the 2022 Sale Agreement for aggregate net proceeds of $ ~~189~~ **310** . ~~0~~ **9** million, after payment of cash commissions to the Sales Agent and approximately $ 0. ~~1~~ **5** million related to legal, accounting and other fees in connection with the sales. In addition, sales of a substantial number of shares of our outstanding 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 of common stock intend to sell shares, could reduce the market price of our common stock. ~~Persons who were~~ **Given the volatility in the capital markets, we may not be willing** ~~our~~ **or able** ~~stockholders prior~~ to ~~our IPO~~ continue to ~~hold~~ **raise equity capital through " at- the- market " offerings. We may, therefore, need to turn to other sources of funding that may have terms that are not favorable to us, or reduce our business operations given capital constraints. In addition, sales of** a substantial number of shares of our **outstanding** common stock ~~that many of them are now able to sell~~ in the public market **could occur at any time** . ~~Significant portions of these~~ **These sales, or the perception in the market that the holders of a large number of** shares ~~are held by a relatively small number~~ of **common stock intend to sell** ~~stockholders. Sales by our stockholders of a substantial number of~~ shares, ~~or the expectation that such sales may occur,~~ could ~~significantly~~ reduce the market price of our common stock **. We cannot predict the effect that future sales of common stock**

or other equity- related securities would have on the market price of our common stock. Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid. Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to the Sales Agent at any time throughout the term of the Sale Agreement. The number of shares that are sold by the Sales Agent after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with the Sales Agent in any instruction to sell shares, and the demand for our common stock during the sales period. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares or the gross proceeds to be raised in connection with those sales, if any, that will be ultimately issued . Risks Related to our Charter and Bylaws Anti- takeover provisions in our charter documents and under Delaware law could make an acquisition of us difficult, limit attempts by our stockholders to replace or remove our current management and adversely affect our stock price. Provisions of our certificate of incorporation and by- laws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our stock. Among other things, the certificate of incorporation and by- laws: • permit the board of directors to issue up to 5, 000, 000 shares of preferred stock, with any rights, preferences and privileges as they may designate; • provide that the authorized number of directors may be changed only by resolution of the board of directors; • provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum; • divide the board of directors into three classes; • provide that a director may only be removed from the board of directors by the stockholders for cause; • require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders, and may not be taken by written consent; • provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner, and meet specific requirements as to the form and content of a stockholder' s notice; • prevent cumulative voting rights (therefore allowing the holders of a plurality of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose); • require that, to the fullest extent permitted by law, a stockholder reimburse us for all fees, costs and expenses incurred by us in connection with a proceeding initiated by such stockholder in which such stockholder does not obtain a judgment on the merits that substantially achieves the full remedy sought; • provide that special meetings of our stockholders may be called only by the chairman of the board, our chief executive officer (or president, in the absence of a chief executive officer) or by the board of directors; and • provide that stockholders will be permitted to amend the bylaws only upon receiving at least two- thirds of the total votes entitled to be cast by holders of all outstanding shares then entitled to vote generally in the election of directors, voting together as a single class. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with any " interested " stockholder for a period of three years following the date on which the stockholder became an " interested " stockholder. Our certificate of incorporation and by- laws designate certain courts as the sole and exclusive forums for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees. Our certificate of incorporation and by- laws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for any state law claims for any derivative action or proceeding brought on our behalf alleging state law claims, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our by- laws, any action to interpret, apply, enforce, or determine the validity of our certificate of incorporation or bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine (the " Delaware Forum Provision "). The Delaware Forum Provision does not apply to claims arising under the Exchange Act or the Securities Act. Our by- laws further provide that the U. S. District Court for the District of Massachusetts will be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (the " Federal Forum Provision "). We have chosen the U. S. District Court for the District of Massachusetts as the exclusive forum for such Securities Act causes of action because our principal executive offices are located in Cambridge, Massachusetts. Our by- laws provide that any person or entity purchasing or otherwise acquiring any interest in any shares of our common stock is deemed to have notice of and consented to the foregoing Delaware Forum Provision and the Federal Forum Provision. The Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders in pursuing the claims identified above, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts. Additionally, the Delaware Forum Provision and the Federal Forum Provision may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the Delaware Forum Provision and the Federal Forum Provision to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition. The Court of Chancery of the State of Delaware or the U. S. District Court for the District of Massachusetts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us

than our stockholders. Risks Related to Tax Matters Changes in tax law may adversely affect our business and financial condition. The laws and rules dealing with U. S. federal, state and local income taxation are routinely being reviewed and modified by governmental bodies, officials and regulatory agencies, including the Internal Revenue Service and the U. S. Treasury Department. Since we were founded in 2014, many such changes have been made and changes are likely to continue to occur in the future. We cannot predict whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or issued, that could result in an increase in our or our stockholders' tax liability. Our ability to use our net operating loss (" NOL ") carryforwards and certain other tax attributes may be limited. We have incurred substantial losses during our history and do not expect to become profitable in the near future, and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. As of December 31, ~~2022~~ **2023**, we had federal and state NOLs of $ ~~852~~ **954**. ~~1~~ **0** million and $ ~~797~~ **922**. 8 million, respectively, some of which begin to expire in 2034. Federal and certain state NOLs generated in taxable years ending after December 31, 2017 are not subject to expiration. As of December 31, ~~2022~~ **2023**, we had federal and state research and development and other credit carryforwards of approximately $ ~~63~~ **100**. ~~4~~ **7** million and $ ~~48~~ **64**. ~~0~~ **1** million, which begin to expire in 2034 and 2029, respectively. Under Sections 382 and 383 of the Code, if a corporation undergoes an " ownership change, " generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three- year period, the corporation' s ability to use its pre- change NOLs, and other pre- change tax attributes (such as research and development tax credits) to offset its post- change income or taxes may be limited. During 2022, we completed an assessment of the available net operating loss carryforwards and other tax attributes under Section 382 **that covered the period from inception through December 31, 2022**. This analysis ~~is~~ **did** not ~~expected to~~ result in a material limitation to our other tax attributes **. We have not completed an analysis through December 31, 2023. To the extent there was a change in control during 2023, our tax attributes could be subject to limitation**. We may experience ownership changes in the future. As a result, if we earn net taxable income, our ability to use our pre- change NOLs and research and development tax credits to offset such taxable income and income tax, respectively, could be subject to limitations. Similar provisions of state tax law may also apply. As a result, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes.