Risk Factors Comparison 2025-03-13 to 2024-03-21 Form: 10-K

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

You should consider carefully the following risk factors, together with all of the other information included in this Annual Report. Each of these risk factors, either alone or taken together, could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our common stock. There may be additional risks that we do not presently know of or that we currently believe are immaterial which could also impair our business and financial position. RISKS RELATED TO THE DISCOVERY AND DEVELOPMENT OF PRODUCT CANDIDATES The approach we are taking to discover and develop drugs is novel and may never lead to marketable products. We have concentrated our therapeutic product research and development efforts on microRNA technology, and our future success depends on the successful development of this technology and products based on our microRNA product platform. Neither we, nor any other company, has received regulatory approval to market therapeutics targeting microRNAs. The scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. If we do not successfully develop and commercialize product candidates based upon our technological approach, we may not become profitable and the value of our common stock may decline. Further, our focus solely on microRNA technology for developing drugs as opposed to multiple, more proven technologies for drug development increases the risks associated with the ownership of our common stock. If we are not successful in developing any product candidates using microRNA technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy. We may not be successful in our efforts to identify or discover potential product candidates. The success of our business depends primarily upon our ability to identify, develop and commercialize microRNA therapeutics. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including: • our research methodology or that of any future collaboration partner may be unsuccessful in identifying potential product candidates; • potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval; or • any future collaboration partners may change their development profiles for potential product candidates or abandon a therapeutic area. If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Preclinical and clinical studies of our product candidates may not be successful. If we are unable to generate successful results from our preclinical and clinical studies of our product candidates, or experience significant delays in doing so, our business may be materially harmed. We have invested a significant portion of our efforts and financial resources in the identification and development of product candidates that target microRNAs. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following: • successfully designing preclinical studies which may be predictive of clinical outcomes; • successful results from preclinical and clinical studies; • receipt of marketing approvals from applicable regulatory authorities; • obtaining and maintaining patent and trade secret protection for future product candidates; • establishing and maintaining manufacturing relationships with third parties or establishing our own manufacturing capability; and • successfully commercializing our products, if and when approved, whether alone or in collaboration with others. If we do not, or any future collaboration partners do not, achieve one or more of these factors in a timely manner or at all, we or any future collaboration partners could experience significant delays or an inability to successfully complete the development of, or commercialize, our product candidates, which would materially harm our business ~~. For example, in July 2022, we received notification from Sanofi of its decision to terminate the HERA trial of RG- 012 for failure to meet Sanofi' s pre- defined futility criteria. In January 2023, we received notification from Sanofi of its decision to terminate the collaboration in its entirety~~ . Preclinical studies, even if successful, may not lead to successful clinical trials and results in early- stage clinical trials may not be predictive of successful results in later stage clinical trials. If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates. Before obtaining marketing approval from regulatory authorities for the sale of product candidates, we or a collaboration partner must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical trials are expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products. Events which may result in a delay or unsuccessful completion of clinical development include: • delays in reaching an agreement with the FDA or other regulatory authorities on final trial design; • imposition of a clinical hold of our clinical trial operations or trial sites by the FDA or other regulatory authorities; • delays in

reaching agreement on acceptable terms with prospective CROs and clinical trial sites; • our inability to adhere to clinical trial requirements directly or with third parties such as CROs; • delays in obtaining required institutional review board approval at each clinical trial site; • delays in recruiting suitable patients to participate in a trial; • delays in the testing, validation, manufacturing and delivery of the product candidates to the clinical sites; • delays in having patients complete participation in a trial or return for post- treatment follow- up; • delays caused by patients dropping out of a trial due to protocol procedures or requirements, product side effects or disease progression; • clinical sites dropping out of a trial to the detriment of enrollment; • time required to add new clinical sites; or • delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials. For example, in July 2018, we voluntarily paused our Phase 1 MAD clinical trial for RGLS4326 due to unexpected observations in our 27- week mouse chronic toxicity study, which was designed to support the Phase 2 **pivotal** ~~proof- of- concept~~ clinical trial in ADPKD previously planned to start in mid- 2019. The observations in the mouse chronic toxicity study were unexpected, given the favorable safety profile of RGLS4326 in previous non- **good laboratory practices ("** GLP **")** and GLP toxicity studies at the same or similar doses supporting the IND and Phase 1 clinical trial. In July 2019, the FDA notified us of additional nonclinical data requirements and placed the IND on a partial clinical hold, formalizing the specific requirements to initiate the MAD study and further proceed into chronic dosing. In October 2021, we announced we would discontinue development of RGLS4326 and would instead prioritize ~~RGLS8429~~ **farabursen** , targeting miR- 17. Additionally, in July 2022, we received notification from Sanofi of its decision to terminate the HERA trial of RG- 012 for failure to meet Sanofi' s pre- defined futility criteria. In January 2023, we received notification from Sanofi of its decision to terminate the collaboration in its entirety. In addition, enrollment and retention of patients in clinical trials could be disrupted by man- made or natural disasters, public health pandemics or epidemics or other business interruptions. If we or any future collaboration partners are required to conduct additional clinical trials or other testing of any product candidates beyond those that are originally contemplated, are unable to successfully complete clinical trials of any such product candidates or other testing, or if the results of these trials or tests are not positive or are only moderately positive or if there are safety concerns, we or any future collaboration partners may: • be delayed in obtaining marketing approval for our product candidates; • not obtain marketing approval at all; • obtain approval for indications or patient populations that are not as broad as originally intended or desired; • obtain approval with labeling that includes significant use or distribution restrictions or safety warnings; • be subject to additional post- marketing testing requirements; or • have the product removed from the market after obtaining marketing approval. Our product development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. Any inability to successfully complete preclinical and clinical development, whether independently or with a collaboration partner, could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. Any of our product candidates may cause adverse effects (" AEs") or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance. AEs caused by our product candidates could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval. Certain oligonucleotide therapeutics have shown injection site reactions and pro- inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our future product candidates may induce similar AEs. If AEs are observed in any clinical trials of our product candidates, including those that a future collaboration partner may develop under an agreement with us, our or any future collaboration partners' ability to obtain regulatory approval for product candidates may be negatively impacted. Further, if any of our future products, if and when approved for commercial sale, cause serious or unexpected side effects, a number of potentially significant negative consequences could result, including: • regulatory authorities may withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy; • regulatory authorities may require the addition of labeling statements, such as warnings or contraindications; • we may be required to change the way the product is administered or conduct additional clinical trials; • we could be sued and held liable for harm caused to patients; or • our reputation may suffer. Any of these events could prevent us or any future collaboration partners from achieving or maintaining market acceptance of the affected product and could substantially increase the costs of commercializing our future products and impair our ability to generate revenues from the commercialization of these products either on our own or with a collaboration partner. **Interim, topline and preliminary data from our clinical trials and preclinical studies that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data. From time to time, we may publicly disclose preliminary or topline data from our clinical trials and preclinical studies, which is based on a preliminary analysis of then- available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular trial. For example, in January 2025, we announced topline data from an interim analysis of the fourth cohort of our MAD trial of farabursen for ADPKD. 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, the preliminary or topline results that we report may differ from future results of the same trials, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline and preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the data we previously published. As a result, topline and preliminary data should be viewed with caution until the final data are available. From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data from**

clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Adverse differences between preliminary, topline or interim data and final data could significantly harm our business prospects. Further, others, including regulatory authorities, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and the value of our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition. Even if we complete the necessary preclinical studies and clinical trials, we cannot predict whether or when we will obtain regulatory approval to commercialize a product candidate and we cannot, therefore, predict the timing of any revenue from a future product. Neither we nor any collaboration partner can commercialize a product until the appropriate regulatory authorities, such as the FDA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee recommends restrictions on approval or recommends non- approval. In addition, we or a collaboration partner may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. **For example, although we have discussed with FDA the potential for an accelerated approval pathway based on a single pivotal Phase 3 study of farabursen for the treatment of ADPKD, there is no assurance that FDA will ultimately agree that the conditions for accelerated approval have been satisfied, even if such trial is successful. We may attempt to secure approval from the FDA through the use of the accelerated approval pathway. If we are unable to obtain such approval, we may be required to conduct additional clinical trials beyond those that we currently contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary regulatory approvals. Even if we receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post- marketing requirements, the FDA may seek to withdraw any accelerated approval we have obtained. We may seek accelerated approval for farabursen for ADPKD and our other product candidates. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The surrogate biomarker of htTKV has not previously been used to support an accelerated approval by FDA. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor' s agreement to conduct, in a diligent manner, additional confirmatory studies to verify and describe the drug' s clinical benefit. If such post- approval studies fail to confirm the drug' s clinical benefit or are not completed in a timely manner, the FDA may withdraw its approval of the drug on an expedited basis. In addition, the FDA may require a sponsor of a product seeking accelerated approval to have a confirmatory trial underway prior to such approval being granted. Prior to seeking accelerated approval for any of our product candidates, we intend to seek feedback from the FDA and will otherwise evaluate our ability to seek and receive accelerated approval. For example, we held an End of Phase 1 meeting with FDA in December 2024 to discuss the potential for accelerated approval pathway for farabursen. There can be no assurance that after our evaluation of any feedback and other factors we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Furthermore, if we decide to submit an application for accelerated approval for any of our product candidates, there can be no assurance that such application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for any of our product candidates would result in a longer time period to commercialization of such product candidate, if any, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace. We may fail to obtain orphan drug designations from the FDA for our product candidates, and even if we obtain such designations, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity. Regulatory authorities in some jurisdictions, including the United States, may designate biologics or drugs designed to address relatively small patient populations as " orphan**

drugs. ” Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200, 000 in the United States, or a patient population greater than 200, 000 in the United States, where there is no reasonable expectation that the cost of developing the drug or biologic will be recovered from sales in the United States. In the United States, orphan designation entitles a party to financial incentives such as opportunities for grant funding for clinical trial costs, tax advantages and user- fee waivers. In addition, if a product candidate that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. In June 2022, the FDA granted Orphan Drug Designation to farabursen for the treatment of ADPKD, and we may seek additional Orphan Drug Designations for our other product candidates in the future. There can be no assurances that we will be able to obtain such designations. Even if we obtain orphan drug designation for a product candidate, we may not be able to obtain or maintain orphan drug exclusivity for that product candidate. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active ingredients may be approved for the same disease or condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug or biologic for the same disease or condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care, or the manufacturer of the product with orphan exclusivity is unable to maintain sufficient product quantity. Orphan drug designation neither shortens the development or regulatory review time of a drug nor gives the drug or biologic any advantage in the regulatory review or approval process. Even if we obtain regulatory approval for a product candidate, we will still face extensive regulatory requirements and our products may face future development and regulatory difficulties. Even if we obtain regulatory approval in the United States, the FDA may still impose significant restrictions on the indicated uses or marketing of our product candidates, or impose ongoing requirements for potentially costly post- approval studies or post- market surveillance. The holder of an approved **New Drug Application ("** NDA **")** is obligated to monitor and report AEs and any failure of a product to meet the specifications in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws. In addition, drug product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with **current good manufacturing practices ("** GMP **")** and adherence to commitments made in the NDA. If we or a regulatory agency discovers previously unknown problems with a product such as AEs of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we or a future collaboration partner fails to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory agency may: • issue a warning letter asserting that we are in violation of the law; • seek an injunction or impose civil or criminal penalties or monetary fines; • suspend or withdraw regulatory approval; • suspend any ongoing clinical trials; • refuse to approve a pending NDA or supplements to an NDA submitted by us; • seize product; or • refuse to allow us to enter into supply contracts, including government contracts. Moreover, the FDA closely regulates the marketing, labeling, advertising and promotion of pharmaceutical products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. Companies may also share truthful and not misleading information that is otherwise consistent with the labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses. Failure to comply with these requirements can result in significant civil, criminal and administrative penalties. Physicians may prescribe legally available products for uses that are not described in the product’ s labeling and that differ from those tested by us and approved by the FDA made in the physician’ s independent medical judgement. Such off- label uses are common across medical specialties. Physicians may believe that such off- label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer’ s communications on the subject of off- label use of their products. Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our future products and generate revenues. **In addition, the policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our development candidates. For example, the U. S. Supreme Court’ s June 2024 decision in Loper Bright Enterprises v. Raimondo overturned the longstanding Chevron doctrine, under which courts were required to give deference to regulatory agencies’ reasonable interpretations of ambiguous federal statutes. The Loper decision could result in additional legal challenges to regulations and decisions issued by federal agencies, including the FDA, on which we rely. Any such legal challenges, if successful, could have a material impact on our business. Additionally, the Loper decision may result in increased regulatory uncertainty, inconsistent judicial interpretations, and other impacts to the agency rulemaking process, any of which could adversely impact our business and operations We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory**

compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability. We may not be successful in obtaining or maintaining necessary rights to microRNA targets, drug compounds and processes for our development pipeline through acquisitions and in- licenses. Presently, we have rights to the intellectual property, through licenses from third parties and under patents that we own, to modulate only a subset of the known microRNA targets. Because our programs may involve a range of microRNA targets, including targets that require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in- license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in- license any compositions, methods of use, processes or other third- party intellectual property rights from third parties that we identify. The licensing and acquisition of third- party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third- party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. For example, we may collaborate with U. S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution' s rights in technology resulting from the collaboration. ~~Regardless of such right of first negotiation~~ **For example, pursuant to our collaboration with UTSW related to products targeting miR- 17** for ~~intellectual property~~ **the treatment of ADPKD, we exercised an option to negotiate a license with UTSW and acquired the Patent Rights and Technology Rights pursuant to the UTSW Agreement. Although we were able to successfully negotiate a license with USTW** , we may be unable to negotiate a license **with any other academic institutions** within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third- party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third- party intellectual property rights, our business, financial condition and prospects for growth could suffer. We may use our financial and human resources to pursue a particular research program ~~or ,~~ product candidate **or clinical development strategy** and fail to capitalize on programs ~~or ,~~ product candidates **or clinical development strategies** that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and human resources, we may have to pursue collaboration agreements for the development and commercialization of our programs and potential product candidates in indications with potentially large commercial markets, while focusing our internal development resources and any internal sales and marketing organization that we may establish on research programs and product candidates for selected smaller markets, such as orphan diseases. As a result, we may forego or delay pursuit of opportunities with other programs or product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement **. In addition, we may allocate financial resources to a particular clinical development strategy that may be costly when more efficient clinical development strategies are available. We may also choose to alter our previously announced clinical development strategy, and in such event, there is no guarantee that such revised clinical development strategy will be perceived favorably or will ultimately yield a more successful result** . If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business. We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work- related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. RISKS RELATED TO OUR FINANCIAL CONDITION AND NEED FOR ADDITIONAL CAPITAL We will need to raise additional capital to develop our product candidates and implement our operating plans, and if we are unable to do so when needed, we will not be able to complete the development and commercialization of our product candidates. **This Form 10- K includes disclosures regarding management' s assessment of our ability to continue as a going concern as our current liquidity position and recurring losses from operations since inception and negative cash flows from operating activities raise substantial doubt about our ability to continue as a going concern.** As of December 31, ~~2023~~ **2024** , we had approximately $ ~~23~~ **75** . 8 million of cash ~~and ,~~ cash equivalents and **short** ~~we had $ 2. 7 million of outstanding debt obligations (which includes $ 1. 4 million of~~

~~outstanding principal and $ 1. 3 million of final payment and loan amendment fees) under our Term Loan with the Lender, which we borrowed under the Loan Agreement. In March 2024, we raised approximately $ 94. 0 million in net proceeds from the sale of our common stock and non-~~ **term investments** ~~voting convertible preferred stock in a private placement financing, after deducting placement agent and financial advisor fees and other financing expenses. We believe our existing resources will be sufficient to fund our planned operations and expenditures for at least the next 12 months~~ . We will need to raise additional capital ~~in the future~~ to fund our operations, and if we are unable to raise additional capital when needed, we will not be able to continue as a going concern. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our product candidates towards or through clinical trials. We will need to raise additional capital to fund our operations and such funding may not be available to us on acceptable terms, or at all. For the foreseeable future, we expect to rely primarily on equity and / or debt financings to fund our operations. If there is volatility in the equity markets, it may create additional challenges to raising sufficient additional capital through an equity or equity- linked financing. Raising additional capital through the sale of securities could cause significant dilution to our stockholders **. If we raise capital through future debt financings, the debt instruments governing such indebtedness may contain provisions that require us to comply with various covenants such as requiring us to maintain certain minimum cash balances or restricting our ability to dispose of assets, complete a merger or acquisition, incur indebtedness, encumber our assets, pay dividends or make other distributions to our stockholders, make specified investments and engage in transactions with our affiliates. In addition, if such indebtedness is secured against our assets, if we are unable to repay, refinance or restructure our indebtedness when payment is due, the lenders could proceed against the collateral or force us into bankruptcy or liquidation** . Any additional fundraising efforts may divert our management from their day- to- day activities, which may adversely affect our ability to develop and commercialize our product candidates. Our ability to raise additional funds will depend, in part, on the success of our preclinical studies and clinical trials and other product development activities, regulatory events, our ability to identify and enter into licensing or other strategic arrangements, and other events or conditions that may affect our value or prospects, as well as factors related to financial, economic and market conditions, many of which are beyond our control. There can be no assurances that sufficient funds will be available to us when required or on acceptable terms, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to: • significantly delay, scale back or discontinue the development or commercialization of any future product candidates; • seek collaborations, or amend existing collaborations, for research and development programs at an earlier stage than otherwise would be desirable or for the development of programs that we otherwise would have sought to develop independently, or on terms that are less favorable than might otherwise be available; • dispose of technology assets, or relinquish or license on unfavorable terms, our rights to technologies or any future product candidates that we otherwise would seek to develop or commercialize ourselves; • pursue the sale of our company to a third party at a price that may result in a loss on investment for our stockholders; or • file for bankruptcy or cease operations altogether. Any of these events could have a material adverse effect on our business, operating results and prospects. ~~Payments under the instruments governing our indebtedness may reduce our working capital. In addition, a default under our loan and security agreement could cause a material adverse effect on our financial position. In June 2016, we entered into a Loan Agreement with the Lender. Under the terms of the Loan Agreement, the Lender provided us with a $ 20. 0 million Term Loan. Our obligations under the Loan Agreement are secured by a first priority security interest in substantially all of our current and future assets. We have also agreed not to encumber our intellectual property assets, except as permitted by the Loan Agreement. Our required monthly payments to the Lender were comprised of interest only through and including the payment made in December 2022. We resumed making principal payments in January 2023. Under the terms of the Loan Agreement, we are required to maintain a cash balance of no less than $ 5. 0 million. We are in compliance with all Loan Agreement covenants as of the date of the filing of this Form 10- K. Amounts outstanding under the Term Loan mature on May 1, 2024. The Loan Agreement requires us, and any debt arrangements we may enter into in the future may require us, to comply with various covenants that limit our ability to, among other things: • dispose of assets; • complete mergers or acquisitions; • incur indebtedness; • encumber assets; • pay dividends or make other distributions to holders of our capital stock; • make specified investments; and • engage in transactions with our affiliates. These restrictions could inhibit our ability to pursue our business strategies. If we default under our obligations under the Loan Agreement, including as a result of a" material adverse change," the lender could proceed against the collateral granted to it to secure our indebtedness or declare all obligation under the Loan Agreement to be due and payable. The definition of " material adverse change " is broad and includes a material impairment in the value of the collateral securing the Term Loan, a material adverse change in our business, operations, or condition (financial or otherwise), and a material impairment of the prospect of repayment of any portion of the Term Loan. Moreover, the determination by the lender as to whether a " material adverse change " has occurred is not within our control. In certain circumstances, procedures by the lenders could result in a loss by us of all of our equipment and inventory, which are included in the collateral granted to the lenders. If any indebtedness under the Loan Agreement were to be accelerated, there can be no assurance that our assets would be sufficient to repay in full that indebtedness. In addition, upon any distribution of assets pursuant to any liquidation, insolvency, dissolution, reorganization or similar proceeding, the holders of secured indebtedness will be entitled to receive payment in full from the proceeds of the collateral securing our secured indebtedness before the holders of other indebtedness or our common stock will be entitled to receive any distribution with respect thereto. We may incur additional indebtedness in the future. The debt instruments governing such indebtedness may contain provisions that are as, or more, restrictive than the provisions governing our existing indebtedness under the Loan Agreement. If we are unable to repay, refinance or restructure our indebtedness when payment is due, the lenders could proceed against the collateral or force us into bankruptcy or liquidation.~~ We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future. Since inception, our operations have been primarily limited to acquiring and

in- licensing intellectual property rights, developing our microRNA product platform, undertaking basic research around microRNA targets and conducting preclinical and clinical studies for our initial programs. We have not yet obtained regulatory approval for any product candidates. Consequently, any predictions about our future success or viability, or any evaluation of our business and prospects, may not be accurate. We have incurred losses in each year since our inception in September 2007. Our net loss was $ ~~30~~ **46** . **4** ~~0 million and $ 28. 3~~ million for the ~~years~~ - **year** ended December 31, ~~2023~~ **2024** ~~and 2022~~ , ~~respectively~~ **compared to $ 30** . ~~As of~~ **0 million for the year ended** December 31, 2023 **. As of December 31, 2024** , we had an accumulated deficit of $ ~~513~~ **559** . ~~2~~ **6** million. We have devoted most of our financial resources to research and development, including our preclinical and clinical development activities. To date, we have financed our operations primarily through the sale of equity securities and convertible debt, through ~~our~~ **the** Term Loan and from revenue received from our former collaboration partners. The size of our future net losses will depend, in part, on the rate of future expenditures and our ability to obtain funding through equity or debt financings, collaborations or grants. We initiated clinical development of ~~RGLS8429~~ **farabursen** in the second quarter of 2022. Even if we or a future collaboration partner successfully obtains regulatory approval to market a product candidate, our revenues will also depend upon the size of any markets in which our product candidates have received market approval, and our ability to achieve sufficient market acceptance and adequate market share for our products. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we: continue our research and preclinical and clinical development of our product candidates, both independently and under any future collaboration agreements; seek to identify additional microRNA targets and product candidates; acquire or in- license other products and technologies; continue with clinical development of our product candidates; seek marketing approvals for our product candidates that successfully complete clinical trials; ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval; maintain, expand and protect our intellectual property portfolio; hire additional clinical, regulatory, research and administrative personnel; and create additional infrastructure to support our operations and our product development and planned future commercialization efforts. We have never generated any revenue from product sales and may never be profitable. Our ability to generate revenue and achieve profitability depends on our ability, alone or with collaboration partners, to successfully complete the development of, obtain the necessary regulatory approvals for and commercialize product candidates. We do not anticipate generating revenues from sales of products for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in: • identifying and validating new microRNAs as therapeutic targets; • completing our research and preclinical development of product candidates; • initiating and completing clinical trials for product candidates; • seeking and obtaining marketing approvals for product candidates that successfully complete clinical trials; • establishing and maintaining supply and manufacturing relationships with third parties; • launching and commercializing product candidates for which we obtain marketing approval, with a collaboration partner or, if launched independently, successfully establishing a sales force, marketing and distribution infrastructure; • maintaining, protecting and expanding our intellectual property portfolio; and • attracting, hiring and retaining qualified personnel. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to predict the timing or amount of increased expenses and when we will be able to achieve or maintain profitability, if ever. In addition, our expenses could increase beyond expectations if we are required by the FDA or foreign regulatory agencies to perform studies and trials in addition to those that we currently anticipate. Even if one or more of the product candidates that we independently develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. RISKS RELATED TO OUR RELIANCE ON THIRD PARTIES We may depend upon collaborations for the development and eventual commercialization of certain microRNA product candidates. If these collaborations are unsuccessful or are terminated, we may be unable to commercialize certain product candidates and we may be unable to generate revenues from our development programs. We may depend upon third party collaboration partners for financial and scientific resources for the clinical development and commercialization of certain of our microRNA product candidates. These collaborations will likely provide us with limited control over the course of development of a microRNA product candidate, especially once a candidate has reached the stage of clinical development. Our ability to recognize revenues from successful collaborations may be impaired by several factors including: • a collaboration partner may shift its priorities and resources away from our programs due to a change in business strategies, or a merger, acquisition, sale or downsizing of its company or business unit; • a collaboration partner may cease development in therapeutic areas which are the subject of the collaboration; • a collaboration partner may change the success criteria for a particular program or potential product candidate thereby delaying or ceasing development of such program or candidate; • a significant delay in initiation of certain development activities by a collaboration partner will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities; • a collaboration partner could develop a product that competes, either directly or indirectly, with a collaboration product; • a collaboration partner with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product; • a collaboration partner with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements; • a collaboration partner may exercise its rights under the agreement to terminate the collaboration; • a dispute may arise between us and a collaboration partner concerning the research, development or commercialization of a program or product candidate resulting in a delay in milestones, royalty payments or termination of a program and possibly resulting in costly litigation or arbitration which may divert management attention and resources; and • a collaboration partner may use our proprietary information or intellectual property in such a way as to invite litigation from a third party or fail to maintain or prosecute intellectual property rights such that our rights in such property are jeopardized. We rely on third parties to conduct some aspects of our compound formulation, research and preclinical studies, and those third

parties may not perform satisfactorily, including failing to meet deadlines for the completion of such formulation, research or testing. We do not expect to independently conduct all aspects of our drug discovery activities, compound formulation research or preclinical studies of product candidates. We currently rely and expect to continue to rely on third parties to conduct some aspects of our preclinical studies and formulation development. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND- enabling studies and clinical trials are conducted in accordance with the study plan and protocols for the trial. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the necessary preclinical studies to enable us or any future collaboration partners to select viable product candidates for IND submissions and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize such product candidates. We rely on third- party manufacturers to produce our preclinical and clinical product candidates, and we intend to rely on third parties to produce future clinical supplies of product candidates that we advance into clinical trials and commercial supplies of any approved product candidates. Reliance on third-party manufacturers entails risks, including risks that we would not be subject to if we manufactured the product candidates ourselves, including: • the inability to meet any product specifications and quality requirements consistently; • a delay or inability to procure or expand sufficient manufacturing capacity; • manufacturing and product quality issues related to scale- up of manufacturing; • costs and validation of new equipment and facilities required for scale- up; • a failure to comply with ~~cGMP~~ - **GMP** and similar foreign standards; • the inability to negotiate manufacturing or supply agreements with third parties under commercially reasonable terms; • termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; • the reliance on a limited number of sources, and in some cases, single sources for raw materials, such that if we are unable to secure a sufficient supply of these product components, we will be unable to manufacture and sell future product candidates in a timely fashion, in sufficient quantities or under acceptable terms; • the lack of qualified backup suppliers for any raw materials that are currently purchased from a single source supplier; • operations of our third- party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier; • carrier disruptions or increased costs that are beyond our control; • disruptions caused by man- made or natural disasters or public health pandemics or epidemics or other business interruptions; and • the failure to deliver products under specified storage conditions and in a timely manner. Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production. We rely on limited sources of supply for the drug substance of product candidates and any disruption in the chain of supply may cause a delay in developing and commercializing these product candidates. We have established manufacturing relationships with a limited number of suppliers to manufacture raw materials and the drug substance of any product candidate for which we are responsible for preclinical or clinical development. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain. As part of any marketing approval, a manufacturer and its processes are required to be qualified by the FDA prior to commercialization. If supply from the approved vendor is interrupted, there could be a significant disruption in commercial supply. An alternative vendor would need to be qualified through an NDA supplement which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional studies if a new supplier is relied upon for commercial production. Switching vendors may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines. In addition, if any future collaboration partners elect to pursue the development and commercialization of certain programs, we will lose control over the manufacturing of the product candidate subject to the agreement. These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, delay milestone payments owed to us or cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to deliver the required commercial quantities of active pharmaceutical ingredients on a timely basis and at commercially reasonable prices, and we are unable to secure one or more replacement suppliers capable of production in a timely manner at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue. Manufacturing issues may arise that could increase product and regulatory approval costs or delay commercialization. As we scale- up manufacturing of product candidates and conduct required stability testing, product, packaging, equipment and process- related issues may require refinement or resolution in order to proceed with any clinical trials and obtain regulatory approval for commercial marketing. We may identify significant impurities, which could result in increased scrutiny by the regulatory agencies, delays in clinical programs and regulatory approval, increases in our operating expenses, or failure to obtain or maintain approval for product candidates or any approved products. We rely on third parties to conduct, supervise and monitor our clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business. We rely, and any future collaboration partners may rely, on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials. While we will have agreements governing their activities, we have limited influence over their actual performance. We control only certain aspects of our CROs' activities. Nevertheless, we are responsible for ensuring that each of our clinical trials are conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We, any future collaboration partners and our CROs are required to comply with the FDA' s or other regulatory agency' s **current good clinical practices (" **GCPs **")** for conducting, recording and reporting the results of IND- enabling studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The

FDA and non- U. S. regulatory agencies enforce these GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or applicable non- U. S. regulatory agency may require us to perform additional clinical trials before approving any marketing applications for the relevant jurisdiction. Upon inspection, the FDA or applicable non- U. S. regulatory agency may determine that our clinical trials did not comply with GCPs. In addition, our clinical trials will require a sufficiently large number of test subjects to evaluate the safety and effectiveness of a potential drug product. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process. Our CROs will not be our employees, and we will not be able to control whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities which could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for such products and any product candidates that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed. We also rely on other third parties to store and distribute drug products for any clinical trials that we may conduct. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, if approved, producing additional losses and depriving us of potential product revenue. RISKS RELATED TO OUR INTELLECTUAL PROPERTY If we are unable to obtain or protect intellectual property rights related to our future products and product candidates, we may not be able to compete effectively in our markets. We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our future products and product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in- license may fail to result in patents with claims that cover the products in the United States or in other countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found; such prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold or have in- licensed with respect to our programs or product candidates fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. A patent may be challenged through one or more of several administrative proceedings including post- grant challenges, re- examination or opposition before the U. S. ~~PTO~~ **Patent and Trademark Office** or foreign patent offices. Any successful challenge of patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we or any future collaboration partners may develop. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, in certain situations, if we and one or more third parties have filed patent applications in the United States and claiming the same subject matter, an administrative proceeding, known as an interference, can be initiated to determine which applicant is entitled to the patent on that subject matter. Such an interference proceeding provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications, or those of licensors or any future collaboration partners. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of a patent or patent application in such a proceeding may not be successful and, even if successful, may result in substantial costs and distract our management and other employees. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Once the patent life has expired for a product, we may be open to competition from generic medications. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know- how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know- how, information or technology that is not covered by patents. Although each of our employees agrees to assign their inventions to us through an employee inventions agreement, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know- how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. In addition, others may independently discover our trade secrets and proprietary information. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-

patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition. Third- party claims of intellectual property infringement may prevent or delay our development and commercialization efforts. Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits. Numerous U. S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties. Third parties may assert that we are employing their proprietary technology without authorization. There may be third- party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third- party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third- party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all. Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business. We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. For example, our exclusive license agreements with our founding companies, Alnylam and Ionis, provide us with rights to nucleotide technologies in the field of microRNA therapeutics based on oligonucleotides that modulate microRNAs. Some of these technologies, such as intellectual property relating to the chemical modification of oligonucleotides, are relevant to our product candidate development programs. If our license agreements with Alnylam or Ionis are terminated, or our business relationships with either of these companies or our other licensors are disrupted by events that may include the acquisition of either company, our access to critical intellectual property rights will be materially and adversely affected. We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our product candidates, which could harm our business significantly. We cannot provide any assurances that third- party patents do not exist which might be enforced against our future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and / or other forms of compensation to third parties. We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful. Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time- consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing. Our defense in a litigation may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties. We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents.

Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees. RISKS RELATED TO COMMERCIALIZATION OF PRODUCT CANDIDATES We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively. The biotechnology and pharmaceutical industries are intensely competitive. We have competitors ~~both~~ in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Our competitors may have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, drug products that are more effective or less costly than any product candidate that we may develop. Most of our programs are targeted toward indications for which there are approved products on the market or product candidates in clinical development. We will face competition from other drugs currently approved or that will be approved in the future for the same therapeutic indications. Our ability to compete successfully will depend largely on our ability to leverage our experience in drug discovery and development to: • discover and develop therapeutics that are superior to other products in the market; • attract qualified scientific, product development and commercial personnel; • obtain patent and / or other proprietary protection for our microRNA product platform and future product candidates; • obtain required regulatory approvals; and • successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new therapeutics. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. We will not achieve our business plan if the acceptance of any of these products is inhibited by price competition or the reluctance of physicians to switch from existing drug products to our products, or if physicians switch to other new drug products or choose to reserve our future products for use in limited circumstances. The inability to compete with existing or subsequently introduced drug products would have a material adverse impact on our business, financial condition and prospects. Established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in- license novel compounds that could make our product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval or discovering, developing and commercializing product candidates before we do, which would have a material adverse impact on our business. The commercial success of our product candidates will depend upon the acceptance of these product candidates by the medical community, including physicians, patients and healthcare payors. The degree of market acceptance of any product candidates will depend on a number of factors, including: • demonstration of clinical safety and efficacy compared to other products; • the relative convenience, ease of administration and acceptance by physicians, patients and healthcare payors; • the prevalence and severity of any AEs; • limitations or warnings contained in the FDA- approved label for such products; • availability of alternative treatments; • pricing and cost- effectiveness; • the effectiveness of our or any collaborators' sales and marketing strategies; • our ability to obtain hospital formulary approval; • our ability to obtain and maintain sufficient third party coverage and adequate reimbursement; and • the willingness of patients to pay out- of- pocket in the absence of third party coverage. Unless other formulations are developed in the future, we expect our compounds to be formulated in an injectable form. Injectable medications may be disfavored by patients or their physicians in the event drugs which are easy to administer, such as oral medications, are available. If a product is approved, but does not achieve an adequate level of acceptance by physicians, patients and healthcare payors, we may not generate sufficient revenues from such product and we may not become or remain profitable. If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenues. We currently do not have an organization for the sales, marketing and distribution of pharmaceutical products and the cost of establishing and maintaining such an organization may exceed the cost- effectiveness of doing so. In order to market any products that may be approved, we must build our sales, marketing, managerial and other non- technical capabilities or make arrangements with third parties to perform these services. With respect to certain of our current programs as well as future programs, we may rely completely on a collaboration partner for sales and marketing. In addition, we intend to enter into collaborations with third parties to commercialize other product candidates, including in markets outside of the United States or for other large markets that are beyond our resources. Although we intend to establish a sales organization if we are able to obtain approval to market any product candidates for niche markets in the United States, we will also consider the option to enter into collaborations for future product candidates in the United States if commercialization requirements exceed our available resources. This will reduce the revenue generated from the sales of these products. Any future collaboration partners may not dedicate sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective collaborations to enable the sale of our product candidates to healthcare professionals and in geographical regions, including the United States, that will not be covered by our own marketing and sales force, or if our potential future collaboration partners do not successfully commercialize the product candidates, our ability to generate revenues from product sales will be adversely affected. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well- funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies. If we obtain approval to commercialize any approved products outside

of the United States, a variety of risks associated with international operations could materially adversely affect our business. If any product candidates that we develop are approved for commercialization, we may also enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including: • different regulatory requirements for drug approvals in foreign countries; • different payor reimbursement regimes, governmental payors or patient self- pay systems and price controls; • reduced protection for intellectual property rights; • unexpected changes in tariffs, trade barriers and regulatory requirements; • economic weakness, including inflation, or political instability in particular foreign economies and markets; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign taxes, including withholding of payroll taxes; • foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; • workforce uncertainty in countries where labor unrest is more common than in the United States; • production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and • business interruptions resulting from geopolitical actions, including war and terrorism, natural disasters, including earthquakes, typhoons, floods and fires, public health pandemics or epidemics or other business interruptions. Coverage and adequate reimbursement may not be available for our product candidates, which could make it difficult for us to sell products profitably. Market acceptance and sales of any product candidates that we develop will depend on coverage and reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third party payors, such as private health insurers, government payors and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. We cannot be sure that coverage and adequate reimbursement will be available for any future product candidates. Also, inadequate reimbursement amounts may reduce the demand for, or the price of, our future products. Further, one payor' s determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize product candidates that we develop. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. In addition, we cannot be certain if and when we will obtain formulary approval to allow us to sell any products that we may develop and commercialize into our target markets. Obtaining formulary approval from hospitals and from payors can be an expensive and time- consuming process. Failure to obtain timely formulary approval will limit our commercial success. There have been a number of legislative and regulatory proposals to change the healthcare system in the United States and in some foreign jurisdictions that could affect our ability to sell products profitably. These legislative and / or regulatory changes may negatively impact the reimbursement for drug products, following approval. The availability of numerous generic treatments may also substantially reduce the likelihood of reimbursement for our future products. The potential application of user fees to generic drug products may expedite the approval of additional generic drug treatments. We expect to experience pricing pressures in connection with the sale of any products that we develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. If we fail to successfully secure and maintain reimbursement coverage for our future products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our future products and our business will be harmed. In addition, in some non- U. S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the **European Union ("** EU **")** provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the U. S. and generally tend to be priced significantly lower. RISKS RELATED TO OUR BUSINESS OPERATIONS AND INDUSTRY Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel. We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are " at will " employees. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical companies for individuals with similar skill sets. In addition, failure to succeed in preclinical studies and clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive or key employee might impede the progress of our research, development and commercialization objectives. We may need to expand our organization and may experience difficulties in managing this growth, which could disrupt our operations. As of December 31, ~~2023~~ **2024** , we had ~~30~~ **34** employees, all of ~~which~~ **whom** were full- time employees. In the future, we may need to expand our organization. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day- to- day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may

divert financial resources from other projects, such as the development of additional product candidates. Moreover, if our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and / or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth. Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading. We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and non- U. S. regulators, provide accurate information to the FDA and non- U. S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self- dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative sanctions. We may undertake internal restructuring activities that could result in disruptions to our business or otherwise materially harm our results of operations or financial condition. From time to time we may undertake internal restructuring activities as we continue to evaluate and attempt to optimize our cost and operating structure in light of developments in our business strategy and long- term operating plans. For example, we initiated a corporate restructuring in May 2017 and in July 2018, each of which resulted in a reduction in our workforce. Any restructuring activities that we may undertake in the future may result in write- offs or other restructuring charges. There can be no assurance that any restructuring activities that we undertake in the future will achieve the cost savings, operating efficiencies or other benefits that we may initially expect. Restructuring activities may also result in a loss of continuity, accumulated knowledge and inefficiency during transitional periods and thereafter. In addition, internal restructurings can require a significant amount of time and focus from management and other employees, which may divert attention from commercial operations. If any internal restructuring activities we undertake in the future fail to achieve some or all of the expected benefits therefrom, our business, results of operations and financial condition could be materially and adversely affected. Certain current and future relationships with customers and third party payors as well as certain of our business operations may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and information security laws and other privacy and information security laws. If we are unable to comply, or have not fully complied or are perceived to have not fully complied, with such laws, we could face significant penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Our operations may be directly, or indirectly through our relationships with customers, third party payors, healthcare providers, and others subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti- Kickback Statute and the federal False Claims Act. These laws may impact, among other things, our proposed sales, marketing and education programs. The laws and regulations that may affect our ability to operate include, but may not be limited to: • the federal Anti- Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs; • federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to the federal government, including Medicare or Medicaid, that are false or fraudulent; • the federal Health Insurance Portability and Accountability Act of 1996 (" HIPAA"), which created additional federal criminal statutes that prohibit, among other things, executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters; • HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act (" HITECH") and its implementing regulations, which also imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy and security of individually identifiable health information of covered entities subject to the rule, such as health plans, healthcare clearinghouses and certain healthcare providers, as well as their business associates, independent contractors of a covered entity that perform certain services involving the use or disclosure of individually identifiable health information on their behalf and their subcontractors that use, disclose, access, or otherwise process individually identifiable health information **, and their covered subcontractors** ; • the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services (" CMS") information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, and further requires applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members; and • state and foreign law equivalents of each of the above federal laws, such as: anti- kickback and false claims laws which may apply to items or services reimbursed by any third party payor, including commercial insurers; state laws that require

pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; state laws that require the reporting of information related to drug pricing; and state and local laws that require the registration of pharmaceutical sales representatives, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. If our operations are found to be in violation (or perceived to be in violation) of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, litigation, significant civil, criminal and administrative penalties, damages, fines, possible exclusion from Medicare, Medicaid and other government healthcare programs, disgorgement, imprisonment, additional reporting requirements and / or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business, including interrupting or stopping clinical trials, and our results of operations. Recent and future healthcare legislation may further impact our business operations. The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, in March 2010, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the" ACA"), was passed and includes measures to significantly change the way healthcare is financed by both governmental and private insurers. There have been executive, judicial and Congressional challenges **and amendments** to certain aspects of the ACA. ~~While Congress has not passed comprehensive repeal legislation, bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Act, includes a provision which repealed, effective January 1, 2019, the tax- based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or~~ **For example** ~~part of a year that is commonly referred to as the " individual mandate ". In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA- mandated " Cadillac " tax on high- cost employer- sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. On June 17, 2021, the U. S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the " individual mandate " was repealed by Congress. Further~~ , on August 16, 2022, ~~President Biden signed~~ the Inflation Reduction Act of 2022 (" IRA") **was signed** into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the " donut hole " under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out- of- pocket cost and through a newly established manufacturer discount program. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the ~~Biden~~ **second Trump** administration will impact the ACA and our business. Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2 % per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013 and, due to subsequent legislative amendments to the statute, including the Infrastructure Investment and Jobs Act and the Consolidated Appropriations Act of 2023, will remain in effect until 2032, unless additional Congressional action is taken ~~. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years~~ . Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and federal and state legislative activity designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, ~~in July 2021, the Biden administration released an executive order, " Promoting Competition in the American Economy, " with multiple provisions aimed at prescription drugs. In response to Biden' s executive order, on September 9, 2021, the U. S. Department of Health and Human Services (" HHS") released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. In addition,~~ the IRA, among other things, (1) directs **the U. S. Department of Health and Human Services (" HHS ")** to negotiate the price of certain single-source drugs ~~and biologics~~ **that have been on the market for at least 7 years** covered under Medicare **(the " Medicare Drug Price Negotiation Program "),** and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. HHS has and will continue to issue and update guidance as these programs are implemented. These provisions **began to** take effect progressively ~~starting~~ in fiscal year 2023. On August ~~29~~ **15** , ~~2023~~ **2024** , HHS announced the ~~list~~ **agreed- upon prices** of the first ten drugs that **were** ~~will be~~ subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. ~~It is currently unclear how the IRA~~ **On January 17, 2025, HHS selected fifteen additional products covered under Part D for price negotiation in 2025. Each year thereafter more Part B and Part D products** will **become subject** ~~be implemented but is likely~~ to ~~have a significant impact on the pharmaceutical industry. In response to the Biden administration' s October 2022 executive order, on February 14, 2023, HHS released a report outlining three~~ -- **the Medicare Drug Price Negotiation Program** ~~new models for testing by the CMS~~

~~Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future~~. Further, on December 7, 2023, ~~the Biden administration announced~~ an initiative to control the price of prescription drugs through the use of march- in rights under the Bayh- Dole Act **was announced** . On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March- In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march- in rights. While march- in rights have not previously been exercised, it is uncertain if that will continue under the new framework. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. For example, on January 5, 2024, the FDA approved Florida' s Section 804 Importation Program (**"** SIP **"**) proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. We expect that healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and lower reimbursement, and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government- funded programs may result in a similar reduction in payments from private payors. We cannot predict what healthcare reform initiatives may be adopted in the future. Further federal, state and foreign legislative and regulatory developments are likely, and we expect ongoing initiatives to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates. We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. Certain oligonucleotide therapeutics have shown injection site reactions and pro- inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our current and future product candidates may induce similar AEs. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in: • impairment of our business reputation; • withdrawal of clinical trial participants; • costs due to related litigation; • distraction of management' s attention from our primary business; • substantial monetary awards to patients or other claimants; • the inability to commercialize our product candidates; and • decreased demand for our product candidates, if approved for commercial sale. We maintain product liability insurance relating to the use of our therapeutics in clinical trials. However, such insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. We **and the third parties with whom we work** are subject to stringent and evolving U. S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our **(or the third parties with whom we work)** actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation (including class actions), fines and penalties, ~~a disruption~~ **disruptions** of our business operations ~~;~~ **,** reputational harm, loss of revenue or profits, and other adverse business consequences. In the ordinary course of business we collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, **"** processing **"**) personal data and other sensitive and confidential information, including proprietary and confidential business data, trade secrets, intellectual property, data we ~~may~~ collect about trial participants in connection with clinical trials, sensitive third- party data, and employee data (collectively, **"** sensitive data **"**). Our data processing activities ~~may~~ subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contractual requirements, and other obligations relating to data privacy and security. Data privacy and security obligations are stringent and changing, with new data privacy and security laws being proposed or enacted. Preparing for and complying with these obligations requires significant resources and may necessitate changes to our information technologies, systems, and practices and to those of any third parties that process personal data on our behalf. The laws and regulations that may affect our ability to operate include, but may not be limited to: • HIPAA, as amended by HITECH, and their implementing regulations, which imposes certain requirements on certain types of individuals and entities relating to the privacy, security and transmission of certain individually identifiable health information. For more information regarding risks associated with HIPAA, please refer to the section above that discusses risks associated with federal and state healthcare laws and regulations; • the **EU** ~~European Union~~ ' s General Data Protection Regulation (" EU GDPR ") and the United Kingdom GDPR (" UK GDPR"), which contain provisions specifically directed at the processing of health information and, more broadly, imposes significant and complex compliance burdens on processing personal data. Under the EU and UK GDPR, government regulators may impose temporary or definitive bans on data processing, as well as fines of up to 20 million

Euros (**or** 17. 5 million British Pounds under the UK GDPR) or 4 % of annual global revenue, whichever is greater; or private litigation related to the processing of personal data brought by classes of data subjects or consumer protection organizations authorized at law to represent their interests. We anticipate that over time we may expand our business operations to include additional operations in the European Economic Area (" EEA") and the United Kingdom (" UK"), including potentially conducting preclinical and clinical trials and, with such expansion, we would be subject to increased governmental regulation in the European countries in which we might operate, including but not limited to the EU and UK GDPR; • the California Consumer Privacy Act of 2018 ~~as amended by the California Privacy Rights Act of 2020~~ (**" "** ~~" CPRA "), (collectively, "~~ CCPA "), which requires covered companies to provide ~~new~~ disclosures to California residents, including consumers, business representatives, and employees, and requires businesses to provide specific disclosures in privacy notices and honor requests of California residents to exercise certain privacy rights. The CCPA provides for ~~administrative~~ **statutory** fines ~~of up to $ 7, 500 per violation~~ and allows private litigants affected by certain data breaches to recover significant statutory damages. Although there are limited exemptions for clinical trial data under the CCPA, the CCPA ~~and other similar laws~~ may impact (possibly significantly) our business activities ~~depending on how it is interpreted~~, should we become subject to the CCPA in the future. **Numerous** ~~In addition, the CPRA expanded the CCPA' s requirements, including by adding a new right for individuals to correct their~~ **other U** ~~personal information and establishing a new regulatory agency to implement and enforce the law~~. ~~Other~~ **S.** states ~~, such as Virginia and Colorado,~~ have also ~~passed~~ **enacted** comprehensive privacy laws, and similar laws are being considered in several other states, as well as at the federal and local levels. While **many of** these ~~states~~ **state laws**, like the CCPA, ~~also~~ exempt some data processed in the context of clinical trials, these developments further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties ~~upon~~ **with** whom we **work** ~~rely; • new laws governing the privacy of consumer health data, including Washington' s My Health My Data Act (" MHMD"), broadly define consumer health data, place restrictions on processing consumer health data (including imposing stringent requirements for consents), provide consumers certain rights with respect to their health data, and create a private right of action to allow individuals to sue for violations of the law~~. Other states are considering and may adopt similar laws **and** ; ~~and~~ • data breach notification laws, personal data privacy laws, consumer protection laws (e. g., Section 5 of the Federal Trade Commission Act), and other similar laws (e. g., wiretapping laws) enacted by federal, state, and local governments in the United States. As our company grows, we may transfer personal data from Europe and other jurisdictions to the United States or other countries. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular, the EEA and the UK have significantly restricted the transfer of personal data to the United States and other countries whose privacy laws it believes are inadequate. Other jurisdictions may adopt **, or have already adopted,** similarly stringent ~~interpretations of their~~ data localization and cross- border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the United States in compliance with law, such as the EEA ~~and UK' s~~ standard contractual clauses, the UK' s International Data Transfer Agreement / Addendum, and the EU- U. S. Data Privacy Framework and the UK extension thereto (which allows for transfers ~~for~~ **to** relevant U. S.- based organizations who self- certify compliance and participate in the Framework), these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal data to the United States. If there is no lawful manner for us to transfer personal data from the EEA, the UK, or other jurisdictions to the United States, or if the requirements for a legally ~~-~~ compliant transfer are too onerous, we could face significant adverse consequences, including increased exposure to regulatory actions, substantial fines, and injunctions against processing or transferring personal data from Europe or other foreign jurisdictions. The inability to import personal data to the United States could significantly and negatively impact our business operations, including by limiting our ability to conduct clinical trial activities in Europe and elsewhere; limiting our ability to collaborate with parties that are subject to such cross- border data transfer or localization laws; or requiring us to increase our personal data processing capabilities and infrastructure in foreign jurisdictions at significant expense. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators, individual litigants, and activist groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers out of Europe for allegedly violating the EU GDPR' s cross- border data transfer limitations. In addition to data privacy and security laws, we are bound by contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful. We also publish policies, marketing materials, and other statements ~~regarding~~ **concerning** data privacy and security **. Regulators are increasingly scrutinizing these statements,** and if these policies, materials or statements are found to be deficient, lacking in transparency, deceptive, unfair, **misleading** or misrepresentative of our practices, we may be subject to investigation, enforcement actions by regulators, or other adverse consequences. Obligations related to data privacy and security (and individuals' data privacy expectations) are quickly changing, becoming increasingly stringent, and creating uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflict among jurisdictions. Preparing for and complying with these obligations requires us to devote significant resources, which may necessitate changes to our services, information technologies, systems, and practices and to those of any third parties that process personal data on our behalf. In addition, these obligations may require us to change our business model. We may at times fail (or be perceived to have failed) in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties ~~upon~~ **with** whom we ~~rely~~ **work** may fail to comply with such obligations, which could negatively impact our business operations and compliance posture. For example, any failure by a third- party ~~processor~~ **with whom we work** to comply with applicable law, regulations, or contractual obligations could result in adverse effects, including inability to or interruption in our ability to operate our business and proceedings against us by governmental entities or others. If we or the third parties ~~upon which~~ **with whom** we ~~rely~~ **work** fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences, including but not

limited to: government enforcement actions (e. g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class- action claims); additional reporting requirements and / or oversight; bans **or restrictions** on processing personal data (including clinical trial data); orders to destroy or not use personal data; and imprisonment of company officials. Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: loss of customers; interruptions or stoppages in our business operations (including, as relevant, clinical trials); inability to process personal data or to operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or revision or restructuring of our operations. Cybersecurity risks and the failure to maintain the security, confidentiality, integrity, and availability of our information technology systems or data, ~~and~~ those maintained on our behalf **, or those of third parties with whom we work** , could result in material adverse impact to our business, including without limitation regulatory investigations or actions, a material interruption to our operations, including clinical trials, damage to our reputation and / or subject us to costs, fines and penalties or lawsuits. In the ordinary course of business, we and the third parties ~~upon which~~ **with whom** we ~~rely~~ **work** process sensitive data, and, as a result, we and the third parties ~~upon which~~ **with whom** we ~~rely~~ **work** face a variety of evolving threats, including but not limited to ransomware attacks, which could cause security incidents. Cyberattacks, malicious internet- based activity, online and offline fraud, and other similar activities threaten the confidentiality, integrity, and availability of our sensitive data and information technology systems, and those of the third parties ~~upon which~~ **with whom** we ~~rely~~ **work** . Such threats are prevalent and continue to rise, are increasingly difficult to detect, and come from a variety of sources, including traditional computer " hackers, " threat actors, " hacktivists, " organized criminal threat actors, personnel (such as through theft or misuse), sophisticated nation- state and nation- state supported **actors. Some** actors now engage in attacks (including advanced persistent threat intrusions) for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and the third parties ~~upon which~~ **with whom** we ~~rely~~ **work** may be vulnerable to a heightened risk of these attacks, including retaliatory cyber- attacks, that ~~could~~ materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our services. We and third parties **with whom** we **work are** ~~rely on may~~ also ~~be the~~ subject ~~of~~ **to** a variety of evolving threats, including but not limited to social- engineering attacks (including through deep fakes, which may be increasingly more difficult to identify as fake, and phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial- of- service attacks, credential stuffing, credential harvesting, personnel misconduct or error, ransomware attacks, supply- chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, earthquakes, fires, floods, attacks enhanced or facilitated by AI, and other similar threats. Threat actors may continue to develop and use more sophisticated tools and techniques (including AI) that are specifically designed to circumvent security controls, evade detection, and obfuscate forensic evidence, making it more difficult for us to identify, investigate and recover from incidents. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions, delays, or outages in our operations, disruption of clinical trials, loss of data (including data related to clinical trials), loss of income, significant extra expenses to restore data or systems, reputational loss and the diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments (including, for example, if applicable laws or regulations prohibit such payments) **. It may be difficult and / or costly to detect, investigate, mitigate, contain, and remediate a security incident. Our efforts to do so may not be successful. Actions taken by us or the third parties with whom we work to detect, investigate, mitigate, contain, and remediate a security incident could result in outages, data losses, and disruptions of our business. Threat actors may also gain access to other networks and systems after a compromise of our networks and systems** . We rely on a global enterprise software system to operate and manage our business, and our business therefore depends on the continuous, effective, reliable, and secure operation of our computer hardware, software, services, networks, communications, Internet servers and related infrastructure. We rely upon third- party service providers and technologies to operate critical business systems and process sensitive data in a variety of contexts, including, without limitation, third- party providers of cloud- based infrastructure, encryption and authentication technology, employee email, content delivery to customers, and other functions. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If ~~our~~ **the** third ~~- party service providers~~ **parties with whom we work** experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if ~~our~~ **the** third ~~- party service providers~~ **parties with whom we work** fail to satisfy their privacy or security- related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. Similarly, supply chain attacks have increased in frequency and we cannot guarantee that third parties and infrastructure in our supply chain or our third- party partners' supply chains have not been compromised or that they do not contain exploitable defects or bugs that could result in a breach of or disruption to our information technology systems or the third- party information technology systems that support us and our services. ~~Despite security controls we have in place, such attacks are difficult to avoid.~~ Our remote workforce ~~poses~~ **has** increased risks to our information technology systems and data, as employees utilize network connections, computers, and devices outside our premises. Additionally, future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Furthermore, we may discover security issues that were not found during due diligence of such acquired or integrated entities, and it may be difficult to integrate companies into our information technology environment and security program. Any of the aforementioned threats could cause..... obligations may increase our operating costs. While we have implemented security measures designed to protect against a security incident, there can be no assurance that our security measures or those of ~~our~~ **the third** ~~partners~~ **parties with whom we work** will be effective in protecting against a security incident. We take steps **designed** to detect and remediate vulnerabilities, but we may be

unable in the future to detect, anticipate, ~~measure~~ or prevent **such** ~~threats or techniques used to detect or exploit~~ vulnerabilities in our ~~(or our partners')~~ information technology, services **(** ~~, communications~~ or ~~software~~ **those of the third parties with whom we work)** because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after an incident has occurred. ~~Unremediated high risk or critical vulnerabilities pose material risks to our business.~~ Further, we may experience delays in deploying remedial measures **or patches** designed to address ~~any such~~ identified vulnerabilities. ~~Vulnerabilities could be exploited and result in a security incident.~~ Any of the aforementioned threats could cause a security incident,which,in turn,could result in unauthorized access to,damage to,disablement or encryption of,use or misuse of,disclosure of,modification of,destruction of,or loss of our data or our customers' data ~~(or that of the third parties with whom we work)~~ ,or disrupt our ability to provide our services or our service providers' ability to support our services ~~.For example,we have been the target of unsuccessful phishing attempts in the past,and we expect such attempts will continue in the future~~ .As a result,our business could suffer.The integrity and protection of our sensitive data,including employee and personal health information,is critical to our business,and employees and others have a high expectation that we will adequately protect their personal information.We ~~have in the past and~~ may ~~in the future~~ expend significant resources,fundamentally change our business activities and practices,or modify our operations,including our clinical trial activities,or information technology in an effort to protect against security incidents **.We take steps to detect and remediate vulnerabilities,but we may not be able to detect and remediate all vulnerabilities because the threats and techniques used to exploit the vulnerability change frequently and are often sophisticated in nature.Therefore,such vulnerabilities could be exploited but may not be detected until after a security incident has occurred.These vulnerabilities pose material risks to our business** .Applicable data protection laws,privacy policies or other obligations related to data privacy (e.g.contractual obligations,obligations related to membership in industry organizations) may require us to implement specific security measures or use industry- standard or reasonable measures to protect against security measures. ~~Applicable data~~ **The regulatory environment governing information,security and** privacy **is increasingly demanding** and **continues to evolve.Maintaining compliance with applicable information** security **and privacy** obligations may **increase** ~~require us,or our operating costs.~~ ~~we may voluntarily choose,to notify relevant stakeholders,including affected individuals,customers,regulators,and investors,of security incidents,or to implement other requirements,such~~ If we, or a third party ~~upon~~ **with** whom we ~~rely~~ **work** , experience a security incident, or are perceived to have experienced a security incident, we may experience **material** adverse consequences, such as: government enforcement actions that could include investigations, fines, penalties, audits and inspections; additional reporting requirements and / or oversight; restrictions on processing of sensitive data (which could impact our clinical trials ~~or training of our algorithm~~); litigation (including class **- action** claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant **material** consequences may cause customers to stop using our services, deter new customers from using our services, and negatively impact our ability to grow and operate our business. Furthermore, our contracts may not contain limitations of liability, and even where they do, there can be no assurance that the limitations of liability in our contracts would be enforceable or adequate or otherwise protect us from liabilities or damages if we fail to comply with applicable data protection laws, privacy policies or data protection obligations related to information security or security incident. Additionally, we cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or adequately mitigate liabilities or damages with respect to claims, costs, expenses, litigation, fines, penalties, business loss, data loss, regulatory actions or material adverse impacts arising out of our privacy and security practices, processing or security incidents we may experience, or that such coverage will continue to be available on commercially reasonable terms or at all. In addition to experiencing a security incident, third parties may gather, collect, or infer sensitive information about us from public sources, data brokers, or other means that reveals competitively sensitive details about our organization and could be used to undermine our competitive advantage or market position. Changes in funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business. The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and / or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U. S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations. Our business and operations might be disrupted or adversely affected by catastrophic events. Our headquarters are located in San Diego County. We are vulnerable to natural disasters such as earthquakes and wild fires, as well as other events that could disrupt our operations. We do not carry insurance for earthquakes or other natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations. In addition, natural disasters or other catastrophic events in various parts of the world, including interruptions in the supply of natural resources, political and governmental changes, disruption in transportation networks or delivery services, severe weather conditions, wildfires and other fires, explosions,

actions of animal rights activists, terrorist attacks, earthquakes, wars and other geopolitical events (such as the war between Russia and ~~Ukrain~~ **Ukraine** , the state of war between Israel and Hamas and the risk of a larger conflict arising from either war), and public health issues could disrupt our operations or those of our collaborators, contractors and vendors or contribute to unfavorable economic or other conditions that could adversely impact us. Our business could be adversely affected by the effects of health pandemics or epidemics in regions where we or third parties ~~on which~~ **with whom** we ~~rely~~ **work** have significant manufacturing facilities, concentrations of clinical trial sites or other business operations, or materially affect our operations globally, including at our headquarters in San Diego and at our clinical trial sites, as well as the business or operations of our manufacturers, CROs or other third parties with whom we conduct business. Our business may be adversely affected by the effects of health pandemics or epidemics. Such a health pandemic or epidemic may pose the risk that we or our clinical trial subjects, employees, contractors, collaborators and vendors may be prevented from conducting certain clinical trials or other business activities for an indefinite period of time, including due to travel restrictions, quarantines, " stay- at- home " and" shelter- in- place" orders or shutdowns that have been or may in the future be requested or mandated by governmental authorities. These and similar disruptions in our operations could negatively impact our business, operating results and financial condition. In addition, our clinical trial may in the future be affected by health pandemics or epidemics. A future pandemic could negatively affect site initiation and create delays in patient enrollment if a pandemic were to impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to an infectious disease, could be delayed or disrupted, which would adversely impact our clinical trial operations. Our business could be negatively impacted by environmental, social and corporate governance (**"** ESG **"**) matters or our reporting of such matters. There is an increasing focus from certain investors, employees, partners, and other stakeholders concerning ESG matters. We may be, or be perceived to be, not acting responsibly in connection with these matters, which could negatively impact us. Moreover, the SEC has recently proposed, and may continue to propose, certain mandated ESG reporting requirements, such as the SEC' s proposed rules designed to enhance and standardize climate- related disclosures, which, if approved, would significantly increase our compliance and reporting costs and may also result in disclosures that certain investors or other stakeholders deem to negatively impact our reputation and / or that harm our stock price. In addition, we currently do not report our environmental emissions and, absent a legal requirement to do so, we currently do not plan to report our environmental emission. Lack of reporting could result in certain investors declining to invest in our common stock. RISKS RELATED TO OUR COMMON STOCK The market price of our common stock may be highly volatile. Our stock price has historically been, and is expected to continue to be, highly volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following: • adverse results or delays in preclinical studies or clinical trials; • inability to obtain additional funding; • any delay in filing an IND or NDA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA' s review of that IND or NDA; • failure to maintain existing collaborations or enter into new collaborations; • failure of any future collaboration partners to elect to develop and commercialize product candidates under our collaboration agreements or the termination of any programs under our collaboration agreements; • failure by us or our licensors and any future collaboration partners to prosecute, maintain or enforce our intellectual property rights; • failure to successfully develop and commercialize our product candidates; • changes in laws or regulations applicable to our preclinical and clinical development activities, product candidates or future products; • inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices; • adverse regulatory decisions; • changes in the structure of healthcare payment systems; • introduction of new products, services or technologies by our competitors; • failure to meet or exceed financial projections we may provide to the public; • failure to meet or exceed the estimates and projections of the investment community; • the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community; • disruptions caused by man- made or natural disasters, public health pandemics or epidemics or other business interruptions; • announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, any future collaboration partners or our competitors; • disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies; • additions or departures of key scientific or management personnel; • significant lawsuits, including patent or stockholder litigation; • changes in the market valuations of similar companies; • sales of our common stock by us or our stockholders in the future; and • trading volume of our common stock. In addition, companies trading in the stock market in general, and The Nasdaq Capital Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. We may be unable to comply with the applicable continued listing requirements of The Nasdaq Capital Market. Our common stock is currently listed on The Nasdaq Capital Market. In order to maintain the listing of our common stock on The Nasdaq Capital Market, we must satisfy minimum financial and other continued listing requirements and standards, including a minimum closing bid price requirement for our common stock of $ 1. 00 per share and a minimum stockholders' equity requirement of $ 2. 5 million. We have failed to comply with Nasdaq' s minimum bid price requirement and minimum stockholders' equity requirement on multiple occasions during the last several years. Most recently, on August 9, 2021, we received a letter from The Nasdaq Stock Market advising us that for 30 consecutive trading days preceding the date of the letter, the bid price of our common stock had closed below the $ 1. 00 per share minimum price required for continued listing on The Nasdaq Capital Market. Our common stock did not meet the $ 1. 00 minimum bid price for a minimum of 10 consecutive trading days within the 180- day period following the date of the letter. Therefore, we requested and were granted an additional 180- day period to regain compliance with the minimum closing bid price requirement. At our 2022 annual meeting of stockholders, our stockholders approved a reverse split of our common stock. In June 2022, we completed a 1- for- 10 reverse split of our outstanding common stock and we subsequently regained compliance with the minimum bid price requirement. There can be no assurance that we will be able

to maintain compliance with the $ 1. 00 minimum bid price requirement or maintain compliance with the minimum stockholders' equity requirement, or continuously satisfy Nasdaq' s other continued listing standards in the future. If we are ultimately not able to maintain or timely regain compliance with Nasdaq' s continued listing requirements, our common stock will be subject to delisting. In the event that our common stock is delisted from Nasdaq and is not eligible for quotation or listing on another market or exchange, trading of our common stock could be conducted only in the over- the- counter market or on an electronic bulletin board established for unlisted securities such as the Pink Sheets or the OTC Bulletin Board. In such event, it could become more difficult to dispose of, or obtain accurate price quotations for our common stock and there would likely also be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. ~~In addition, the delisting of our common stock from The Nasdaq Capital Market would constitute an event of default under our Loan Agreement.~~ The requirements of being a publicly traded company may strain our resources and divert management' s attention. As a publicly traded company, we have incurred, and will continue to incur, significant legal, accounting and other expenses. In addition, the Sarbanes- Oxley Act, as well as rules subsequently implemented by the SEC and The Nasdaq Capital Market have imposed various requirements on public companies. In July 2010, the Dodd- Frank Wall Street Reform and Consumer Protection Act (the" Dodd- Frank Act") was enacted. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel have devoted and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time- consuming and costly. Changes or modifications in financial accounting standards, including those related to revenue recognition, may harm our results of operations. From time to time, the Financial Accounting Standards Board (" FASB"), either alone or jointly with other organizations, promulgates new accounting principles that could have an adverse impact on our financial position, results of operations or reported cash flows. Any difficulties in adopting or implementing any new accounting standard could result in our failure to meet our financial reporting obligations, which could result in regulatory discipline and harm investors' confidence in us. Finally, if we were to change our critical accounting estimates, including those related to clinical trial and preclinical study accruals, our operating results could be significantly affected. Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall. Substantially all of our outstanding shares of common stock are available for public sale, subject in some cases to volume and other limitations. If our existing stockholders sell substantial amounts of our common stock in the public market, or the market perceives that such sales may occur, the trading price of our common stock could decline. In addition, shares of common stock that are ~~either~~ subject to outstanding options or **restricted stock units,** reserved for future issuance under our employee benefit plans **or issuable upon conversion of our non- voting convertible preferred stock or upon exercise of our outstanding warrants** are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules **, the terms of such non- voting convertible preferred stock or the terms of such outstanding warrants, as applicable,** and Rule 144 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline. 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 our stockholders and could cause our stock price to fall. We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, preferred stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time, any of which may result in material dilution to investors and / or our existing stockholders. New investors could also be issued securities with rights superior to those of our existing stockholders. As of December 31, ~~2023~~ **2024** , warrants to exercise an aggregate of ~~6~~ **1** . ~~2~~ **8** million shares of our common stock were outstanding at **an** ~~a weighted- average~~ exercise price per share of $ 7. ~~76~~ **46** . In addition, as of December 31, ~~2023~~ **2024** , an aggregate of ~~19~~ **37** . ~~7~~ **0** million shares were issuable upon conversion of shares of our Class A- 1, Class A- 2, Class A- 3, Class A- 4 ~~and ,~~ Class A- 5 **and Class A- 6** preferred stock at the option of the holder, subject to beneficial ownership limitations. Pursuant to our 2019 ~~Equity Incentive~~ Plan ~~(the" 2019 Plan")~~ , our management is authorized to grant stock options and other equity- based awards to our employees, directors and consultants. In addition, **beginning on January 1, 2025 through (and including) January 1, 2029,** the number of shares ~~available~~ **authorized** for **issuance** ~~future grant~~ under the 2019 Plan will automatically increase on January 1st **of** each year ~~commencing on January 1, 2021 through January 1, 2029,~~ by 5 **. 0** % of ~~all~~ **the sum of (x) the total number of** shares of **common** ~~our capital~~ stock outstanding **on** ~~as of~~ December 31st of the preceding calendar year ~~, subject to~~ **plus (y)** the ~~ability~~ **total number** of **shares** ~~our board~~ of **common stock issuable upon conversion** ~~directors to take action to reduce the size~~ of **shares of convertible preferred stock outstanding on December 31st of** the ~~increase in~~ **preceding calendar year (without regard to** any ~~given~~ **beneficial ownership limitations applicable thereto) plus (z) the total number of shares of common stock issuable upon cash exercise of prefunded warrants outstanding on December 31st of the preceding calendar** year **(without regard to any beneficial ownership limitations applicable thereto)** . Furthermore, pursuant to our 2022 ~~Employee Stock~~ Purchase Plan ~~(" ESPP")~~ , **certain eligible employees may purchase shares of** our **common** ~~management is authorized to grant~~ stock ~~options and other equity- based awards to our employees~~ . The number of shares available for future ~~grant~~ **issuance under the 2022 Purchase Plan** will automatically increase by a number equal to the lesser of 1 % of the total number of shares of ~~Common~~ **common** ~~Stock~~ **stock** outstanding on December 31st of the preceding calendar year and 50, 000 shares of ~~Common~~ **common** ~~Stock (which number has been adjusted to give effect to the 1- for- 10 reverse~~ stock ~~split of the Common Stock, effected on June 28, 2022)~~ , subject to the ability of our board of directors to take action to reduce the size of the increase in any given year.

Currently, we plan to register the increased number of shares available for issuance under the 2019 Plan and the 2022 ~~ESPP~~ **Purchase Plan** each year. In addition, we adopted an Inducement Plan in 2021 ~~(the " Inducement Plan ")~~ pursuant to which our management has the ability to grant stock options exercisable for up to an aggregate of 1, 030, 000 shares of our common stock to new employees as inducements material to such new employees entering into employment with us. The number of shares which may be granted under the Inducement Plan may be increased in the future by our board of directors. In the event we increase the number of shares which may be granted under the Inducement Plan, or adopt another inducement plan for which no stockholder approval is required under applicable rules and regulations, and grant options pursuant to such plan, our stockholders may experience additional dilution, which could cause our stock price to fall. We may be the subject of putative securities class action litigation in the future. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. For example, certain putative class action complaints were filed against us and certain of our current and former executive officers in January 2017 alleging that the defendants violated the federal securities laws by making materially false and misleading statements regarding our business and the prospects for RG- 101, thereby artificially inflating the price of our securities. On December 29, 2020, the court entered a final judgment and dismissed the action with prejudice. It is possible that additional lawsuits will be filed, or allegations made by stockholders, with respect to these same or other matters and also naming us and / or our officers and directors as defendants. While we carry liability insurance, there is no assurance that any losses we incur in connection with any lawsuits will be covered or that coverage, if any, will be sufficient. In addition, any future litigation could result in substantial costs and a diversion of management' s attention and resources, which could harm our business. Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business, cash flow, financial condition or results of operations. New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Act, the Coronavirus Aid, Relief, and Economic Security Act, and the IRA enacted many significant changes to U. S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to such legislation may affect us, and certain aspects of such legislation could be repealed or modified in future legislation. In addition, it is uncertain if and to what extent various states will conform to federal tax legislation. Future tax reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one- time charges, and could increase our future U. S. tax expense. Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited. As of December 31, ~~2023~~ **2024**, we had net operating loss (" NOL") carryforwards for U. S. federal and California state tax purposes of $ ~~389~~ **405** . ~~5~~ **2** million and $ 146. 3 million, respectively. A portion of the federal and California state NOL carryforwards will begin to expire, if not utilized, in 2030 ~~and 2033, respectively~~ . ~~NOLs~~ **NOL carryforwards** that expire unused will be unavailable to offset future income tax liabilities. ~~Under current law, federal~~ **Federal** NOLs incurred in taxable years beginning after December 31, 2017 of $ ~~126~~ **141** . ~~1~~ **8** million will carry forward indefinitely, but the deductibility of such federal ~~NOLs~~ **NOL carryforwards in a tax year** is limited to 80 % of taxable income **in such year** ~~. It is uncertain if and to what extent various states will conform to federal tax laws~~ . In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the" Code"), and corresponding provisions of state law, if a corporation undergoes an " ownership change, " which is generally defined as a greater than 50 % change (by value) in its equity ownership by" 5- percent shareholders" over a three- year period, the corporation' s ability to use its pre- change NOL carryforwards and other pre- change tax attributes (such as research tax credits) to offset its post- change income or taxes may be limited. We have determined that we triggered an " ownership change " limitation at the completion of our initial public offering in October 2012 and in July 2015. **We have** ~~The Company has~~ not performed a Section 382 ownership- change analysis through December 31, ~~2023~~ **2024**, and it is possible there may have been additional ownership changes. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. As a result, if we earn net taxable income, our ability to use our pre- ownership change NOL carryforwards to offset U. S. federal taxable income will be subject to limitations, which could harm our future operating results by effectively increasing our future tax obligations. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed **. For example, California imposed limits on the usability of California state net operating losses to offset taxable income in tax years beginning after 2023 and before 2027** . As a result, if we earn net taxable income, we may be unable to use all or a material portion of our NOL carryforwards and other tax attributes, which could potentially result in increased future tax liability to us and adversely affect our future cash flows. We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock. We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. In addition, our ability to pay cash dividends is currently prohibited by the terms of our secured debt, and any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Any return to stockholders will therefore be limited to the appreciation of their stock. Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management. Some provisions of our charter documents and Delaware law may have anti- takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management. These provisions include: • authorizing the issuance of " blank check " preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval; • prohibiting stockholder action by written

consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; • eliminating the ability of stockholders to call a special meeting of stockholders; • establishing the state of Delaware as the sole forum for certain legal actions against the Company, its officers and directors; and • establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings. In addition, we are subject to 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 an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change in control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us. GENERAL RISK FACTORS Unstable market, economic and geopolitical conditions may have serious adverse consequences on our business, financial condition and stock price. The global credit and financial markets in the past have experienced, and may in the future experience, extreme volatility and disruptions. These disruptions can result in severely diminished liquidity and credit availability, increases in inflation, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment, high inflation, high interest rates, bank failures, or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our operations, growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic downturn, exposure to a bank failure, or rising inflation, which could directly affect our ability to attain our operating goals on schedule and on budget. Other international and geo- political events could also have a serious adverse impact on our business. For instance, in February 2022, Russia initiated military action against Ukraine and the two countries are now at war. In response, the United States and certain other countries imposed significant sanctions and trade actions against Russia and could impose further sanctions, trade restrictions, and other retaliatory actions. Additionally, in October 2023, Hamas initiated an attack against Israel, provoking a state of war and **subsequently** ~~the risk of~~ a larger **regional** conflict. While we cannot predict the broader consequences, these conflicts and retaliatory and counter- retaliatory actions could materially adversely affect global trade, currency exchange rates, inflation, regional economies, and the global economy, which in turn may increase our costs, disrupt our supply chain, impair our ability to raise or access additional capital when needed on acceptable terms, if at all, or otherwise adversely affect our business, financial condition, and results of operations.