Risk Factors Comparison 2024-11-26 to 2023-11-29 Form: 10-K

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The Company' s business involves various risks and uncertainties in addition to the normal risks of business, some of which are discussed in this section. It should be noted that the Company' s business may be adversely affected by general economic conditions and other forces beyond the Company' s control. In addition, other risks and uncertainties not presently known or that the Company currently believes to be immaterial may also adversely affect the Company' s business. Any such risks or uncertainties, or any of the following risks or uncertainties, that develop into actual events could result in a material and adverse effect on the Company' s business, financial condition, results of operations, or liquidity. The information discussed below should be considered carefully with the other information contained in this Annual Report on Form 10- K and the other documents and materials filed by the Company with the SEC, as well as news releases and other information publicly disseminated by the Company from time to time. Risk Factors Summary Risks Related to Our Discovery, Development, and Commercialization of Medicines • Our prospects substantially depend on the success of our clinical- stage product candidates. If we and our licensees are unable to obtain approval for and commercialize these product candidates, our business could be materially harmed. • There are substantial risks inherent in attempting to commercialize our new drugs, and, as a result, we may not be able to successfully develop products for commercial use. • Our product candidates are in clinical development, which is a lengthy and expensive process with uncertain outcomes and the potential for substantial delays. There can be no assurance that our product candidates will obtain regulatory approval, which is necessary before they can be commercialized. • Our clinical trials may not yield successful results for the product candidates that we may identify and pursue for their intended uses, which would prevent, delay or limit the scope of regulatory approval and commercialization. • Our clinical trials may reveal significant adverse events, toxicities or other side effects and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates. • Results of earlier studies or clinical trials may not be predictive of future clinical trial results, and initial studies or clinical trials may not establish an adequate safety or efficacy profile for our product candidates to justify proceeding to advanced clinical trials or an application for regulatory approval. • We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for a product candidate and may have to limit its commercialization. • The successful commercialization of our product candidates, if approved, will depend in part on the extent to which government authorities and health insurers establish adequate reimbursement levels and pricing policies. **• Our commercialization, collaborative and other arrangements may give rise to disputes over commercial terms, contract interpretation and ownership or protection of our intellectual property and may adversely affect the commercial success of our products.** Risks Related to Regulatory Review and Approval of Our Candidates • A Fast Track product designation may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval. • We and our licensees conduct clinical trials for product candidates outside the United States, and the FDA and comparable foreign regulatory authorities may not accept data from such trials. • Even if we obtain FDA approval for products in the United States, we may never obtain approval to commercialize any product candidates outside of the United States, which would limit our ability to realize their full market potential. • Even if our product candidates are approved for commercialization, failure to comply with regulatory requirements or unanticipated problems with our products may result in various adverse actions such as the suspension or withdrawal of one or more of our products, closure of a facility or enforcement of substantial penalties or fines **. • Pharmaceutical and biological product marketing is subject to substantial regulation in the U. S. and any failure by us or our commercial and collaborative partners to comply with applicable statutes or regulations can adversely affect our business** . Risks Related to Our Intellectual Property • Our ability to protect our patents and other proprietary rights is uncertain, exposing us to the possible loss of competitive advantage. • We are party to technology license agreements with third parties that require us to satisfy obligations to keep them effective and, if these agreements are terminated, our technology and our business could be seriously and adversely affected. ~~• We may be subject to patent infringement claims, which could result in substantial costs and liability and prevent us from commercializing our potential products. • We may not be able to effectively secure first- tier technologies when competing against other companies or investors.~~ Risks Related to Our Business Model • Our business model assumes we will generate revenue by, among other activities, marketing or out- licensing the products we develop. Our drug candidates are in various stages of development and we have no approved products based on RNA interference and our delivery technologies. Accordingly, there is a limited amount of information about us upon which you can evaluate our business and prospects. • We may need to establish additional relationships with strategic and development partners to fully develop our drug candidates and market any approved products. • Our ability to generate milestone and royalty payments under our current and potential future licensing and collaboration agreements is substantially controlled by our partners, and as such, we will likely need other sources of financing to continue to develop our internal drug candidates. • We may lose a considerable amount of control over our intellectual property and may not receive anticipated revenues in strategic transactions, particularly where the consideration is contingent on the achievement of development or sales milestones. • We will need to achieve commercial acceptance of our drug candidates to generate revenues and achieve profitability **. • If the market opportunities for our approved product candidates, if any, are smaller than we expect, it could materially adversely affect our financial condition and results of operations** . • We have limited manufacturing capability and must rely on third- party manufacturers to manufacture our clinical supplies and commercial products, if and when approved, and if they fail to meet their obligations, the development and commercialization of our products could be adversely affected. • We rely on third parties to conduct our clinical trials, and if

they fail to fulfill their obligations, the development of our products may be adversely affected. • We face competition from various entities including large pharmaceutical companies, small biotech companies, private companies, and research institutions. • We may have difficulty expanding our operations successfully as we evolve our pipeline and move toward commercializing drugs. • Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected. • Our operations, including our relationships with healthcare providers, physicians and third- party payers, are subject to applicable anti- kickback, fraud and abuse, and other healthcare laws and regulations, which, in the event of a violation, exposes us to liability for criminal sanctions, civil penalties, and contractual damages, and reputational harm and diminished profits and future earnings. **• The actions of distributors and specialty pharmacies could affect our ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such distributors and specialty pharmacies could adversely affect our revenues, financial condition, or results of operations.** Risks Related to Our Financial Condition • We have a history of net losses, and we expect to continue to incur net losses and may not achieve or maintain profitability. • We will require substantial additional funds to complete our research and development activities **. • The terms of our Sixth Street Financing Agreement and our indebtedness could adversely affect our operations and limit our ability to plan for or respond to changes in our business. If we are unable to comply with restrictions in our Sixth Street Financing Agreement, the repayment of our existing indebtedness could be accelerated** . • If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements prove inaccurate, our actual results may vary from those reflected in our accruals. • Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance. • The investment of our cash, cash equivalents and fixed income securities is subject to risks which may cause losses and affect the liquidity of these investments. • Our ability to utilize net operating loss carryforwards and other tax benefits may be limited. Risks Related to Investment and Securities • If securities or industry analysts do not publish research reports about our business or if they make adverse recommendations regarding an investment in our stock, our stock price and trading volume may decline. • The market for purchases and sales of our common stock may be limited, and the sale of a limited number of shares could cause the price to fall sharply. • Our common stock price has fluctuated significantly over the last several years and may continue to do so in the future, without regard to our results of operations and prospects. Economic and Industry Risks • Drug development is time consuming, expensive and risky ~~. • The healthcare system is under significant financial pressure to reduce costs, which could reduce payment and reimbursement rates for drugs~~ . • Regulatory standards are subject to change over time, making it difficult to accurately predict the likelihood of marketing approval even when clinical trials meet their endpoints. Our future success is substantially dependent on the ability of our company and our licensees to timely complete clinical trials and obtain marketing approval for, and then successfully commercialize our clinical- stage product candidates. We are not permitted to market or promote our product candidates before we receive marketing approval from the FDA and comparable foreign regulatory authorities, and we may never receive such marketing approvals. The success of developing and commercializing our product candidates will depend on several factors, including the following: • obtaining positive data that supports demonstration of efficacy, safety and tolerability profiles and durability of effect for our product candidates that are satisfactory to the FDA or any comparable foreign regulatory authority for marketing approval; • successful and timely enrollment of appropriate patients for the indications included in our current and future clinical trials; • potential variability of patient outcomes; • the extent of any required post- marketing approval commitments to applicable regulatory authorities; • the establishment of and maintenance of sufficient internal manufacturing capabilities; • the maintenance of existing or the establishment of new supply arrangements with third- party drug product suppliers and manufacturers for clinical development and, if approved, commercialization of our product candidates; • the maintenance of existing or the establishment of new scaled production arrangements with third- party manufacturers to obtain finished products that are appropriately packaged for sale; • obtaining and maintaining patent protection, trade secret protection and regulatory exclusivity, both in the United States and internationally; • protecting our rights in our intellectual property portfolio, including our licensed intellectual property; • establishing sales, marketing and distribution capabilities and the successful launch of commercial sales of our product candidates if and when approved for marketing, whether alone or in collaboration with others; • a continued acceptable safety profile following any marketing approval; • commercial acceptance by patients, the medical community and third- party payors; and • our ability to compete with other therapies. We do not have complete control over many of these factors, including certain aspects of clinical development and the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any collaborator or licensee. For development programs that are licensed to third parties, we generally do not have control over the design or conduct of clinical trials and will not have discretion over marketing decisions. If we are not successful with respect to one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize any product candidates from our lead programs, which would materially harm our business. If we do not receive marketing approvals for such product candidates, we may not be able to continue our operations. Scientific research and development requires significant amounts of capital and takes a long time to reach commercial viability if it can be achieved at all. To date, our research and development projects have not produced commercially viable drugs and may never do so. During the research and development process, we may experience technological barriers that we may be unable to overcome. Because we use platform technology to develop drug candidates, toxicology signals that may emerge in the course of testing of one particular candidate may apply broadly across our drug candidate platform. Further, certain underlying premises in our development programs are not proven and many of the drug targets that we are pursuing have not yet been validated clinically. For instance, ARO- RAGE has demonstrated the ability to reduce the expression of RAGE in the lung, however it has not been established that this will have an anti- inflammatory effect sufficient for a meaningful clinical benefit in patients with inflammatory lung disease. Further, it is also unknown at this time what may be required to gain favorable

reimbursement. With respect to fazirsiran, it is also unknown at this time what changes in the liver may be required to gain regulatory approval and / or favorable reimbursement for a drug that reduces the production of mutant alpha- 1 antitrypsin in the liver. Similar uncertainties and risks exist that are specific to each of our development programs. Because of these and similar uncertainties, it is possible that no commercial products will be successfully developed. If we are unable to successfully develop commercial products, we will be unable to generate revenue or build a sustainable or profitable business. The sale of human therapeutic products in the United States and foreign jurisdictions is subject to extensive and time- consuming regulatory approval which requires, among other things: • controlled research and human clinical testing; • establishment of the safety and efficacy of the product; • government review and approval of a submission containing manufacturing, preclinical and clinical data; and • adherence to cGMP regulations during production and storage. Since 2011, we have focused substantially all of our efforts and financial resources on identifying, acquiring and developing our product candidates, including conducting lead optimization, nonclinical studies, preclinical studies and clinical trials, and providing general administrative support for these operations. And, the clinical- stage product candidates we currently have under development will require significant development, preclinical and clinical testing and investment of significant funds to gain regulatory approval before they can be approved for commercialization. The results of our research and human clinical testing of our products may not meet regulatory requirements. Some of our product candidates, if approved, may require the completion of post- market studies. There can be no assurance that any of our products will be further developed and approved. The process of completing clinical testing and obtaining required approvals will take several years and require the use of substantial resources. For instance, we currently plan to study plozasiran in a cardiovascular outcomes trial, and cardiovascular outcomes trials are expensive clinical trials performed in a large number of subjects over several years. Further, there can be no assurance that product candidates employing a new technology will be shown to be safe and effective in clinical trials or receive applicable regulatory approvals. If we fail to obtain regulatory approvals for any or all of our products, we will not be able to market such product and our operations may be adversely affected. We must demonstrate our product candidates' safety and efficacy in humans for each target indication through extensive clinical testing. We may experience numerous unforeseen events during, or as a result of, the testing process that could delay or prevent commercialization of any products, including the following: • the results of preclinical studies may be inconclusive, or they may not be indicative of results that will be obtained in human clinical trials; • safety and efficacy results attained in early human clinical trials may not be indicative of results that are obtained in later clinical trials; • after reviewing test results, we may abandon projects that we might previously have believed to be promising; • we or our regulators may suspend or terminate clinical trials because the participating subjects or patients are being exposed to unacceptable health risks; and • our product candidates may not have the desired effects or may include undesirable side effects or other characteristics that preclude regulatory approval or limit their commercial use if approved. We cannot be certain that current clinical trials or any future clinical trials, whether conducted by us or our licensees, will be successful. Additionally, any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications, which could have a material adverse effect on our business, financial condition and results of operation. Success in clinical trials in a particular indication does not ensure that a product candidate will be successful in other indications. Similarly, approval of a product candidate in a particular indication does not ensure that the product candidate will be successful in other indications. For instance, **although** ~~even if~~ plozasiran ~~'~~**'** s Phase 3 **PALISADE** trial for patients with FCS ~~is~~ **was** successful in achieving its **primary endpoint and all multiplicity- controlled key secondary** endpoints **, and we filed** ~~and~~ **an** ~~a~~ **NDA with the FDA on November 16, 2024 and sought regulatory approval with additional global regulatory authorities thereafter, there can be no guarantee that the FDA or another** regulatory authority approves plozasiran for the treatment of FCS, **and** plozasiran may not succeed in achieving its clinical trial endpoints or be approved for the treatment of larger indications such as sHTG or ASCVD because the endpoints and clinical data required for approval in a rare disease indication are different from what is required for a broader patient population. Moreover, results acceptable to support approval in one jurisdiction may be deemed inadequate by another regulatory authority to support regulatory approval in that other jurisdiction. To the extent that the results of the trials are not satisfactory to the FDA or comparable foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates. Even if regulatory approval is secured for a product candidate, the terms of such approval may limit the scope and use of the specific product candidate, which may also limit its commercial potential. In order to obtain marketing approval for any of our product candidates, we must demonstrate the safety and efficacy of the product candidate for the relevant clinical indication or indications through preclinical studies and clinical trials as well as additional supporting data. As is the case with pharmaceuticals generally, it is likely that there may be side effects and adverse events (" AEs ") associated with the use of our products or product candidates. If our product candidates are associated with undesirable side effects in preclinical studies or clinical trials, or have unexpected characteristics, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective. If further significant adverse events or other side effects are observed in any of our current or future clinical trials, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of that product candidate altogether. We, the FDA, the EMA, other applicable regulatory authorities or an institutional review board may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early- stage studies have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the drug from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability relative to other

therapies. Any of these developments could materially harm our business, financial condition and prospects. Clinical trials of our product candidates may not uncover all possible adverse events that patients may experience. Clinical trials are conducted in representative samples of the potential patient population, which may have significant variability. By design, clinical trials are based on a limited number of subjects and are of limited duration of exposure to the product, to determine whether the product candidate demonstrates the substantial evidence of efficacy and safety necessary to obtain regulatory approval. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered. It may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration may a more complete safety profile be identified. Further, even larger clinical trials may not identify rare significant AEs, and the duration of such studies may not be sufficient to identify when those events may occur. Other products have been approved by the regulatory authorities for which safety concerns have been uncovered following approval. Such safety concerns have led to labeling changes, restrictions on distribution through use of a REMS, or withdrawal of products from the market, and any of our product candidates may be subject to similar risks. Although to date our current drug candidates have generally evidenced an acceptable safety profile in clinical trials, patients treated with our products, if approved, may experience previously unreported adverse reactions or minor incidences of adverse reactions may manifest with greater frequency in subsequent larger trials, and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If toxicities, adverse events or any other safety problems occur or are identified after our products, if any, reach the market, we may make the decision or be required by regulatory authorities to conduct additional clinical safety trials, amend the labeling of our products or add additional warnings to the labeling, recall our products, or even withdraw approval for our products. Topline data may not accurately reflect the complete results of a particular study or trial. We may publicly disclose topline or interim data from time to time, which is based on a preliminary analysis of then- available efficacy and safety data which are based on preliminary analysis of key efficacy and safety 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 study or trial. 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 topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimations, 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 drug candidate or drug and our company in general. In addition, the information we may 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 drug, drug candidate or our business. If the topline data that we report differ from a future analysis of results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for and commercialize our product candidates, our business, operating results, prospects or financial condition may be harmed. The results of nonclinical and preclinical studies and clinical trials may not be predictive of the results of later- stage clinical trials, and interim results of clinical trials do not necessarily predict final results. The results of preclinical studies and clinical trials in one set of patients or disease indications, or from preclinical studies or clinical trials that we did not lead, may not be predictive of those obtained in another. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. In addition, preclinical and clinical data are often susceptible to various 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. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through nonclinical studies and initial clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late- stage clinical trials after achieving positive results in early- stage development, or after achieving positive results in pivotal trials, and we cannot be certain that we will not face similar setbacks. Even if early- stage clinical trials are successful, we may need to conduct additional clinical trials of our product candidates in additional patient populations or under different treatment conditions before we are able to seek approvals from the FDA and regulatory authorities outside the United States to market and sell these product candidates. Our failure to obtain marketing approval for our product candidates for commercially viable indications, or at all, would substantially harm our business, prospects, financial condition and results of operations. It may take us longer than we project to complete clinical trials, and we may not be able to complete them at all. Although for planning purposes we project the commencement, continuation and completion of our clinical trials, a number of factors, including scheduling conflicts with participating clinicians and clinical institutions, and difficulties in identifying or enrolling patients who meet trial eligibility criteria, may cause significant delays. Enrollment of clinical trials may be particularly difficult in orphan diseases or limited- sized patient populations. The FDA or other regulatory bodies may require additional, longer or broader clinical trials to establish safety and effectiveness, notwithstanding guidance the Company may have received from those bodies during clinical trial planning and execution. Further, the cost for conducting clinical trials is significant and if our cash resources become limited we may not be able to commence, continue and / or complete our clinical trials. We may not commence or complete clinical trials involving any

of our product candidates as projected or may not conduct them successfully. The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by clinical trial participants, consumers, healthcare providers, pharmaceutical companies, or others selling our products. If we cannot successfully defend ourselves against these claims, we may incur substantial liabilities. Regardless of merit or eventual outcomes of such claims, product liability claims may result in: • decreased demand for our product candidates; • impairment of our business reputation; • withdrawal of clinical trial participants; • costs of litigation; • substantial monetary awards to patients or other claimants; and • loss of revenues. Our insurance coverage may not be sufficient to reimburse us for all 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. Sales of any approved drug candidate will depend in part on the availability of coverage and reimbursement from third- party payers such as government insurance programs, including Medicare and Medicaid, private health insurers, health maintenance organizations and other health care related organizations, who are increasingly challenging the price of medical products and services. Accordingly, coverage and reimbursement may be uncertain. Adoption of any drug by the medical community may be limited if third- party payers will not offer adequate coverage. Additionally, significant uncertainty exists as to the reimbursement status of newly- approved drugs. Cost control initiatives may decrease coverage and payment levels for any drug and, in turn, the price that we will be able to charge and / or the volume of our sales. We are unable to predict all changes to the coverage or reimbursement methodologies that will be applied by private or government payers. Any denial of private or government payer coverage or inadequate reimbursement could harm our business and reduce our revenue. With respect to our partnered product candidates, we will be reliant on that partner to obtain reimbursement from government and private payors for the drug, if approved, and any failure of that partner to establish adequate reimbursement could have a negative impact on our revenues and profitability. In addition, both the federal and state governments in the United States and foreign governments continue to propose and pass new legislation, regulations, and policies affecting coverage and reimbursement rates, which are designed to contain or reduce the cost of health care. Further federal and state proposals and healthcare reforms are likely, which could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunity. For example, the IRA includes several measures intended to lower the cost of prescription drugs and related healthcare reforms, including limits on price increases and subjecting an escalating number of drugs to annual price negotiations with CMS (The Centers for Medicare & Medicaid Services). We cannot be sure whether additional legislation or rulemaking related to the IRA will be issued or enacted, or what impact, if any, such changes will have on the profitability of any of our drug candidates, if approved for commercial use, in the future. There also may be future changes unrelated to the IRA that result in reductions in potential coverage and reimbursement levels for our product candidates, if approved and commercialized, and we cannot predict the scope of any future changes or the impact that those changes would have on our operations. If future reimbursement for approved product candidates, if any, is substantially less than we project, or rebate obligations associated with them are substantially greater than we expect, our future net revenue and profitability could be materially diminished. We may not enjoy the market exclusivity benefits of our orphan drug designations. Although we may obtain orphan designations in the treatment of certain diseases our products are intended to treat, the designation may not be applicable to any particular product we might get approved and that product may not be the first product to receive approval for that indication. Under the Orphan Drug Act, the first product with an orphan designation receives market exclusivity, which prohibits the FDA from approving the " same " drug for the same indication. The FDA has stated that drugs can be the " same " even when they are not identical but has not provided guidance with respect to how it will determine " sameness " for RNAi drugs. It is possible that another RNAi drug could be approved for the treatment of a disease that one of our orphan products is intended to treat before our product is approved, which means that we may not obtain orphan drug exclusivity and could also potentially be blocked from approval until the first product' s orphan drug exclusivity period expires or we demonstrate, if we can, that our product is superior. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved and granted orphan drug exclusivity, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Further, orphan drug exclusivity can be lost if the FDA later determines that the request for designation was materially defective or if the applicant is unable to assure the availability of sufficient quantities of the drug to meet the needs of patients with the disease or condition for which the drug was designated. Our success depends on the attraction and retention of senior management and scientists with relevant expertise. Our future success depends to a significant extent on the continued services of our key employees, including our senior scientific, technical and managerial personnel. We do not maintain key person life insurance for any of our executives and we do not maintain employment agreements with many senior employees. Competition for qualified employees in the pharmaceutical industry is high, and our ability to execute our strategy will depend in part on our ability to continue to attract and retain qualified scientists, management and other employees. This will depend in part on our ability to create and maintain a desirable workplace culture, which may be impacted by employee preferences for remote working. In addition, the market for qualified employees in the pharmaceutical industry is experiencing labor shortages and inflationary pressures are causing salaries and wages to increase, all of which exacerbates these competitive dynamics. If we are unable to find, hire and retain qualified individuals, we will have difficulty implementing our business plan in a timely manner, or at all.

Our commercialization, collaborative and other arrangements may give rise to disputes over commercial terms, contract interpretation and ownership or protection of our intellectual property and may adversely affect the commercial success of our product candidates. We have in the past and may again in the future enter into collaboration or license arrangements, including commercialization or collaborative arrangements, some of which may be based on less definitive agreements, such as memoranda of understanding, material transfer agreements, options or feasibility

agreements. Commercialization and collaborative relationships are generally complex and can give rise to disputes regarding the relative rights, obligations and revenues of the parties, including the ownership of intellectual property and associated rights and obligations, especially when the applicable collaborative provisions have not been fully negotiated and documented. Such disputes have arisen in the past from time to time and, if they arise again could delay collaborative research, development or commercialization of potential product candidates, and can lead to lengthy, expensive litigation or arbitration. The terms of such arrangements may also limit or preclude us from commercializing products or technologies developed pursuant to such collaborations. Additionally, the commercialization or collaborative partners under these arrangements might breach the terms of their respective agreements or fail to maintain, protect or prevent infringement of the licensed patents or our other intellectual property rights by third parties. Moreover, negotiating commercialization and collaborative arrangements often takes considerably longer to conclude than the parties initially anticipate, which could cause us to enter into less favorable agreement terms that delay or defer recovery of our development costs and reduce the funding available to support key programs. Any failure by our commercialization or collaborative partners to abide by the terms of their respective agreements with us (including their failure to accurately calculate, report or pay any royalties payable to either us or a third party or their failure to repay, in full or in part, either any outstanding receivables or any other amounts for which we are entitled to reimbursement) may adversely affect our results of operations. We are not always able to enter into commercialization or collaborative arrangements on acceptable terms, which can harm our ability to develop and commercialize our current and potential future products and technologies. Other factors relating to collaborations that may adversely affect the commercial success of our product candidates include: • any parallel development by a commercialization or collaborative partner of competitive technologies or products; • arrangements with commercialization or collaborative partners that limit or preclude us from developing products or technologies; • premature termination of a commercialization or collaboration agreement or the inability to renegotiate existing agreements on favorable terms; or • failure by a commercialization or collaborative partner to devote sufficient resources to the development and commercial sales of products using our current and potential future products and technologies. Our commercialization or collaborative arrangements do not necessarily restrict our commercialization or collaborative partners from competing with us or restrict their ability to market or sell competitive products. Our current and any future commercialization or collaborative partners may pursue existing or other development- stage products or alternative technologies in preference to those being commercialized or developed in collaboration with us. In addition, contract disputes with customers or other third parties may arise from time to time. Our commercialization or collaborative partners, or customers or other third parties, may also terminate their relationships with us or otherwise decide not to proceed with the development, commercialization or purchase of our product candidates. Risks Related to Regulatory Review and Approval of Our Product Candidates Breakthrough Therapy designation for **Plozasiran and / or** Fazirsiran (formerly ARO- AAT) may not lead to a faster development or review process. We have been granted a Breakthrough Therapy designation for **plozasiran in the United States for the treatment of FCS and** fazirsiran in the United States for the treatment of liver disease associated with AATD. Breakthrough Therapy designation is intended to facilitate the development and expedite the review of new therapies to treat serious conditions with unmet medical needs by providing sponsors with the opportunity for frequent interactions and additional drug development guidance with the FDA and its senior managers. Breakthrough Therapy designation applies to the combination of the drug candidate and the specific indication for which it is being studied. Product candidates that receive Breakthrough Therapy designation may receive more frequent interactions with the FDA regarding the product candidate' s development plan and clinical trials and may be eligible for the FDA' s Rolling Review. Despite receiving Breakthrough Therapy designation, **plozasiran and / or** fazirsiran may not actually benefit from faster clinical development or regulatory review or approval any sooner than other product candidates that do not have such designation, or at all. Furthermore, such a designation does not increase the likelihood that **plozasiran or** fazirsiran will receive marketing approval in the United States. The FDA may also rescind Breakthrough Therapy designation if it determines that **plozasiran or** fazirsiran no longer meets the relevant criteria. A Fast Track product designation may not lead to faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval. We have received a Fast Track product designation for plozasiran in the United States for the treatment of FCS, and we may seek Fast Track designation for other of our current or future product candidates. The Fast Track designation is a program offered by the FDA designed to facilitate drug development and to expedite the review of new drugs that are intended to treat serious or life- threatening conditions. Compounds selected must demonstrate the potential to address unmet medical needs. The FDA' s Fast Track designation allows for close and frequent interaction with the FDA. A designated Fast Track drug may also be considered for priority review with a shortened review time, rolling submission, and accelerated approval if applicable. A Fast Track designation does not, however, guarantee FDA approval or expedited approval of any application for the product candidate. The receipt of such a designation for a product candidate may not result in a faster development process, review, or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate marketing approval by the FDA. In addition, the FDA may later decide that the products no longer meet the designation conditions. We intend to deliver some of our product candidates via drug delivery devices that will have their own regulatory, development, supply and other risks. We intend to deliver some of our product candidates via drug delivery devices, such as an autoinjector or nebulizer. There may be unforeseen technical complications related to the development activities required to bring such a product to market, including container compatibility and / or dose volume requirements **. If our product candidates are intended to be used with drug delivery devices, we expect to utilize drug delivery devices authorized for marketing under clearances of approvals held by third parties** . Our product candidates may not be approved or may be substantially delayed in receiving approval if the devices do not gain and / or maintain their own regulatory approvals or clearances. Where approval

of the drug product and device is sought under a single application, the increased complexity of the review process may delay approval. In addition, some drug delivery devices are provided by single- source unaffiliated third- party companies. We may be dependent on the sustained cooperation and effort of those third- party companies both to supply the devices and, in some cases, to conduct the studies required for approval or other regulatory clearance of the devices. Even if approval is obtained **for our products** , we may also be dependent on those third- party companies continuing to maintain such approvals or clearances **, if required, for their drug delivery devices** once they have been received. Failure of third- party companies to supply the devices, to successfully complete studies on the devices in a timely manner, or to obtain or maintain required approvals or clearances of the devices could result in increased development costs, delays in or failure to obtain regulatory approval and delays in product candidates reaching the market or in gaining approval or clearance for expanded labels for new indications. We and our licensees currently conduct clinical trials outside the United States. The acceptance by the FDA or comparable foreign regulatory authority of study data from clinical trials conducted outside the United States or another jurisdiction may be subject to certain conditions or may not be accepted at all. In cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U. S. population and U. S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and (iii) the data may be considered valid without the need for an on- site inspection by the FDA or, if the FDA considers such as inspection to be necessary, the FDA is able to validate the data through an on- site inspection or other appropriate means. Additionally, the FDA' s clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA or any comparable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. Most of our clinical trials involve study subjects outside of the United States, including most of our phase 1 clinical trials (which often enroll study subjects in Australia and New Zealand), and our Phase 3 clinical trials of plozasiran, for which we have enrolled (with respect to FCS **and sHTG**) and plan to enroll (with respect to ~~sHTG and~~ ASCVD) cohorts outside the United States. If the FDA or any comparable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time- consuming and delay aspects of our business plan, and which may result in product candidates that we may develop not receiving approval or clearance for commercialization in the applicable jurisdiction. Even if we obtain FDA approval for products in the United States, we may never obtain approval to commercialize any product candidates outside of the United States, which would limit our ability to realize their full market potential. In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and effectiveness. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional or different administrative review periods from those in the United States, including additional preclinical studies or clinical trials. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval before a product can be marketed in that jurisdiction, even after establishing safety and efficacy in a clinical setting. Seeking foreign regulatory approval could result in difficulties and costs and require additional nonclinical studies or clinical trials which could be costly and time- consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our product candidates in those countries. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We do not have any product candidates approved for sale in international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approval in international markets is delayed, our target market will be reduced and our ability to realize the full market potential of our products will be harmed. If regulatory approval to sell any of our product candidates is received, regulatory agencies will subject any marketed product (s) and the facilities where they are manufactured to continual review and periodic inspection. If previously unknown problems with a product, manufacturing and laboratory facilities or regulatory requirements are discovered, such as adverse events of unanticipated severity or frequency, problems with a manufacturing process or laboratory facility, or failure to comply with applicable regulatory approval requirements, a regulatory agency may impose restrictions or penalties on that product or on us. Such restrictions or penalties may include, among other things: • restrictions on the marketing or manufacturing of the product, the withdrawal of the product from the market or product recalls; • warning **, untitled, or it has come to our attention** letters **,** or holds on clinical trials; • refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of approvals; • product seizure or detention, or refusal to permit the import or export of our product candidates; and • closure of the facility, enforcement of substantial fines, injunctions, or the imposition of civil or criminal penalties. **Any marketing activities associated with our product candidates, if approved for commercialization, will be subject to numerous federal and state laws governing the marketing and promotion of pharmaceutical and biological products. The FDA regulates post- approval promotional labeling and advertising to ensure that they conform to statutory and regulatory requirements. In addition to FDA restrictions, the marketing of prescription drugs is subject to laws and regulations prohibiting fraud and abuse under government healthcare programs. Similarly, many states have similar statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, and, in some states, such statutes or regulations apply regardless of the payor. In addition, government authorities may also seek to hold us responsible for any failure of our commercialization or collaborative partners to comply with applicable statutes or regulations. If we, or our commercial or collaborative**

partners, fail to comply with applicable FDA regulations or other laws or regulations relating to the marketing of our product candidates, if approved for commercialization, we could be subject to criminal prosecution, civil penalties, seizure of products, injunctions and exclusion of our product candidates from reimbursement under government programs, as well as other regulatory or investigatory actions against our future product candidates, our commercial or collaborative partners or us. See also " Our operations, including our relationships with healthcare providers, physicians and third- party payers, are subject to applicable anti- kickback, fraud and abuse, and other healthcare laws and regulations, which, in the event of a violation, exposes us to liability for criminal sanctions, civil penalties, and contractual damages, and reputational harm and diminished profits and future earnings. " We have licensed rights to patents and have filed and expect to continue to file patent applications. Researchers sponsored by us may also file patent applications that we may need to license. Such patent applications may not be available for licensing or may not be economically feasible to license. Certain of our patents may not be granted or may not contain claims of the necessary breadth because, for example, prior patents exist. If a particular patent is not granted, the value of the invention described in the patent would be diminished. Further, even if these patents are granted, they may be difficult to enforce. Even if ultimately successful, efforts to enforce our patent rights could be expensive, distracting for management, cause our patents to be invalidated or held unenforceable, and thus frustrate commercialization of products. Even if patents are issued and are enforceable, others may develop similar, superior or parallel technologies to any technology developed by us and not infringe on our patents. Our technology may prove to infringe upon patents or rights owned by others. Patent prosecution and maintenance is expensive, and we may be forced to curtail prosecution or maintenance if our cash resources are limited. Thus, the patents held by or licensed to us may not afford us any meaningful competitive advantage. In addition, the laws of some foreign countries in which we do business, including through our joint ventures, do not protect intellectual property rights to the same extent or in the same manner as the laws of the United States. Moreover, if we or our licensors fail to maintain the patents and patent applications covering our product candidates or technologies, including as a result of geopolitical events such as civil or political unrest (including the ongoing conflicts between Ukraine and Russia and Israel and Palestine), we may not be able to use such patents and patent applications or stop a competitor from marketing products that are the same as or similar to our product candidates. 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 adequately protect our owned intellectual property or derive sufficient value from our licensed or owned intellectual property, the value of your investment may decline. In addition, patent grant standards by the USPTO and its foreign counterparts are not always uniform or predictable, and subject to change. For example, the America Invents Act enacted a number of changes to U. S. patent laws, which may prevent us from adequately protecting our inventions and discoveries, including our ability to seek injunctive relief, pursue infringement claims, and obtain substantial damage awards. An example of a major provision of the America Invents Act is the change in the U. S. patent policy from a first- to- invent to a first- to- file practice. **Additionally, the USPTO and patent offices in other jurisdictions have often required that patent applications directed to pharmaceutical and / or biotechnology- related inventions be limited or narrowed substantially to cover only the specific innovations exemplified in the patent application, thereby limiting the scope of protection against competitive challenges. Accordingly, even if we or our licensors are able to obtain patents, the patents might be substantially narrower than anticipated. Thus, there is no assurance as to the degree and range of protections any of our patents, if issued, may afford us or whether patents will be issues.** Foreign counterparts to this law are also not uniform, and there is no worldwide policy governing the subject matter and scope of claims granted in a pharmaceutical or biotechnology patent. Uncertainty, arising from changing laws, can impact our ability to protect our patents and other proprietary rights. We are party to license agreements to incorporate third- party proprietary technologies into our drug products under development **or our manufacturing processes** . These license agreements require us to pay royalties and satisfy other conditions. If we fail to satisfy our obligations under these agreements, the terms of the licenses may be materially modified, such as by rendering currently exclusive licenses non- exclusive, or may give our licensors the right to terminate their respective agreement with us, which could limit our ability to implement our current business plan and harm our business and financial condition **. We may be subject to patent infringement claims, which could result in substantial costs and liability and prevent us from commercializing our potential products** . Because the intellectual property landscape in the fields in which we participate is rapidly evolving and interdisciplinary, it is difficult to conclusively assess our freedom to operate without infringing on third- party rights. However, if granted marketing approval, we are currently aware of certain patent rights held by third parties that, if found to be valid and enforceable, could be alleged to render one or more of our drug candidates infringing. If a claim should be brought and is successful, we may be required to pay substantial damages, be forced to abandon any affected drug candidates and / or seek a license from the patent holder. In addition, any patent infringement claims brought against us, whether or not successful, may cause us to incur significant expenses and divert the attention of our management and key personnel from other business concerns. These could negatively affect our results of operations and prospects. We cannot be certain that patents owned or licensed by us will not be challenged, potentially successfully, by others. In addition, if our product candidates are found to infringe the intellectual property rights of third parties, these third parties may assert infringement claims against our customers, licensees and other parties with whom we have business relationships, and we may be required to indemnify those parties for any damages they suffer as a result of these claims. The claims may require us to initiate or defend protracted and costly litigation on behalf of customers, licensees, and other parties regardless of the merits of these claims. If any of these claims succeed, we may be forced to pay damages on behalf of those parties or may be required to obtain licenses for the products they use. If we cannot obtain all necessary licenses on commercially reasonable terms, we may be unable to continue selling such products. We license patent rights from third- party owners and we rely on such owners to obtain, maintain and enforce the patents underlying such licenses. We are a party to a number of licenses that give us rights to third- party intellectual property that is necessary or useful for our business. We also expect to enter into additional licenses to third- party

intellectual property in the future. Our success may depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications to which we are licensed. Even if patents are issued in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. Our technology licensed from various third parties may be subject to retained rights. Our licensors often retain certain rights under their agreements with us, including the right to use the underlying technology for noncommercial academic and research use, to publish general scientific findings from research related to the technology, and to make customary scientific and scholarly disclosures of information relating to the technology. It is difficult to monitor whether our licensors limit their use of the technology to these uses, and we could incur substantial expenses to enforce our rights to our licensed technology in the event of misuse. Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information. In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers, and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. As our organization grows, so does the risk of unauthorized disclosure of confidential information. In addition, while we undertake efforts to protect our trade secrets and other confidential information from disclosure, others may independently discover trade secrets and proprietary information, and in such cases, we may not be able to assert any trade secret rights against such party. **Enforcing a claim that a party illegally obtained and is using our trade secrets is challenging and the outcome is unpredictable. In addition, courts outside of the U. S. may be less willing to protect trade secrets.** Costly and time- consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position **. We may not be able to effectively secure first- tier technologies when competing against other companies or investors** . Our future success may require that we acquire patent rights and know- how to new or complimentary technologies. However, we also compete with a substantial number of other companies that are working to develop novel drugs using technology that compete directly with us. We are aware of several other companies that are working to develop RNAi therapeutic products and any one of these companies may develop its RNAi technology more rapidly and more effectively than us ~~,~~ may also compete for technologies we desire. In addition, many venture capital firms and other institutional investors, as well as other pharmaceutical and biotech companies, invest in companies seeking to commercialize various types of emerging technologies. Many of these companies have greater financial, scientific and commercial resources than us. Therefore, we may not be able to secure the technologies we desire or to otherwise effectively compete. Furthermore, should any commercial undertaking by us prove to be successful, there can be no assurance competitors with greater financial resources will not offer competitive products and / or technologies. We may not be able to protect our intellectual property rights throughout the world, which could negatively impact our business. Filing, prosecuting and defending patents covering our current and any future product candidates in all countries throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we or our licensors have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we may obtain patent protection but where patent enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued or licensed patents, and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from competing. Issued patents may be challenged by third parties in the courts or patent offices in various countries throughout the world. Invalidation proceedings may result in patent claims being narrowed, invalidated or held unenforceable. Uncertainties regarding the outcome of such proceedings, as well as any resulting losses of patent protection, could harm our business. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. Some countries do not enforce patents related to medical treatments, or limit enforceability in the case of a public emergency. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected. The intellectual property systems in other countries can be destabilized or unpredictable as a result of geopolitical events such as civil or political unrest (including the ongoing conflicts between Ukraine and Russia and Israel and Palestine). Therefore, during such geopolitical events, the ability to obtain, retain and enforce intellectual property protection in the affected countries may be uncertain and evolve during the course of such geopolitical event. The U. S. government' s response to geopolitical events may also negatively affect our ability to obtain, retain and enforce intellectual property protection in the affected countries. Uncertainties regarding geopolitical events, as well as any resulting losses of intellectual property protection, could harm our business ~~. Our business model assumes we will generate revenue by, among other activities, marketing or out- licensing the products we develop. Our drug candidates are in various stages of development and we have no approved products based on RNA interference and our delivery technologies. Accordingly, there is a limited amount of information about us upon which you can evaluate our business and prospects~~ . We have no approved drugs and thus have not begun to market or generate revenues from the commercialization of any product candidates. Because no drug candidates generated with our product platform have been approved, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to

successfully: • Execute product development activities using technologies that have not yet generated an approved product; • Build, maintain, and protect a strong intellectual property portfolio; • Demonstrate safety and efficacy of our drug candidates in multiple human clinical studies; • Receive FDA approval and approval from similar foreign regulatory bodies; • Gain market acceptance for the development and commercialization of any drugs we develop; • Ensure our products are reimbursed by commercial and / or government payors at a rate that permits commercial viability; • Develop and maintain successful strategic relationships with suppliers, distributors, and commercial licensing partners; • Manage our spending and cash requirements as our expenses will increase in the near term if we add programs and additional preclinical and clinical trials; and • Effectively market any products for which we obtain marketing approval. If we are unsuccessful in accomplishing these objectives, we may not be able to develop products, raise capital, expand our business or continue our operations. Over the past several years we have entered into license and collaboration agreements with Takeda, Janssen, Amgen, Horizon, GSK and Visirna. Our business strategy includes securing additional collaborations with other pharmaceutical and biotech companies to support the development of our RNAi therapeutics and other drug candidates. We do not possess all of the financial and development resources necessary to develop and commercialize all of the products that may result from our technologies. Unless we expand our **own** product development capacity and enhance our **own** internal marketing capability, we may need to make ~~appropriate~~ arrangements with **other** strategic partners to develop and commercialize any drug candidates that may be approved. We may not be able to attract such partners, and even if we are able to enter into such partnerships, the terms may be less favorable than anticipated. Further, entering into partnership agreements may limit our commercialization options and / or require us to share revenues and profits with our partners. If we do not find appropriate partners, or if our existing arrangements or future agreements are not successful, our ability to develop and commercialize products could be adversely affected. Even if we are able to find collaborative partners, the overall success of the development and commercialization of product candidates in those programs will depend largely on the efforts of other parties and will be beyond our control, particularly as partnered programs progress and our licensees may elect to assume greater control over these programs. In addition, in the event we pursue our commercialization strategy through collaboration or licenses to third parties, there are a variety of technical, business and legal risks, including: • We may not be able to control the amount and timing of resources that our collaborators may be willing or able to devote to the development or commercialization of our drug candidates or to their marketing and distribution; and • Disputes may arise between us and our collaborators that result in the delay or termination of the research, development or commercialization of our drug candidates or that result in costly litigation or arbitration that diverts our management' s resources. The occurrence of any of the above events or other related events could impair our ability to generate revenues and harm our business and financial condition. Under our licensing and collaboration agreements with Amgen, ~~Janssen,~~ Takeda ~~,~~ ~~Horizon~~ , GSK and Visirna, our partners substantially control clinical development and commercialization for all of the candidates covered under those agreements in their relevant territories. To the extent that (i) our partners' interests in advancing these candidates or targets changes, (ii) unforeseen scientific issues with the candidates arise, or (iii) the pace at which our partners move the candidates through clinical trials toward commercialization slows, our ability to collect milestones and royalties may be significantly diminished. This would further cause us to rely upon other sources of financing to continue to develop our other internal drug candidates. Our business model has been to develop new technologies and to utilize the intellectual property created through the research and development process to develop commercially successful products. If the acquirers of our technologies fail to achieve performance milestones, we may not receive a significant portion of the total value of any sale, license or other strategic transaction. Even if our research and development efforts yield technologically feasible applications, we may not successfully develop commercial products. Drug development takes years of study in human clinical trials prior to regulatory approval, and, even if we are successful in getting regulatory approval of our drug candidates, it may not be on a timely basis. During our drug development period, superior competitive technologies may be introduced which could diminish or extinguish the potential commercial uses for our drug candidates. Additionally, the degree to which the medical community and consumers will adopt any product we develop is uncertain. The rate and degree of market acceptance of our products will depend on a number of factors, including the establishment and demonstration in the medical community of the clinical efficacy and safety of our products, their potential advantage over alternative treatments, and the costs to patients and third- party payors, including insurance companies and Medicare. Recent efforts in the United States and abroad to reduce overall healthcare spending has put significant pressure on the price of prescription drugs and certain companies have been publicly criticized for the relatively high cost of their therapies. These pressures may force us to sell any approved drugs at a lower price than we or analysts may anticipate or may result in lower levels of reimbursement and coverage from third parties. **Moreover, as no drug candidates generated with our product platform has been approved for commercialization, we have not generated any revenue from product sales. Our ability to generate significant revenue and achieve profitability depends on our ability, alone or with potential strategic collaboration partners, to complete the development of and obtain the regulatory and marketing approvals necessary to commercialize our drug candidates and introduce products that will be accepted by the medical community. The commercial success of our products, if approved, will depend on many factors, including, but not limited to: • the availability of coverage and adequate and timely reimbursement from managed care plans, private insurers, government payors (such as Medicare and Medicaid and similar foreign authorities) and other third- party payors for our products; • patients' ability and willingness to pay out- of- pocket for our products in the absence of coverage and / or adequate reimbursement from third- party payors; • patient demand for our products; • our ability to establish and enforce intellectual property rights in and to our products; and • our ability to avoid third- party patent interference, intellectual property challenges or intellectual property infringement claims.** We cannot predict whether significant commercial market acceptance for our products, if approved, will ever develop, and we cannot reliably estimate the projected size of any such potential market. Our revenue growth and achievement of consistent profitability will depend substantially on our ability to introduce products that will be accepted by the medical community. If we

are unable to cost- effectively achieve acceptance of our technology among the medical establishment and patients, or if the associated products do not achieve wide market acceptance, our business will be materially and adversely affected **. If the market opportunities for our approved product candidates, if any, are smaller than we expect, it could materially adversely affect our financial condition and results of operation. If the market opportunity for our products, if approved, is smaller than we expect, we may never become or remain profitable nor generate sufficient revenue growth to sustain our business even if we obtain significant market share for them. The potentially addressable patient population for our products may be limited or may not be amenable to treatment with our products, and new patients may become increasingly difficult to identify or access, which would adversely affect our results of operations and our business** . We rely on outside sources for various components and processes for our products. We rely on third parties for various components and processes for our product candidates. We may not be able to achieve multiple sourcing because there may be no acceptable second source, other companies may choose not to work with us, or the component or process sought may be so new that a second source does not exist or does not exist on acceptable terms. For instance, many of our pulmonary drug candidates are administered using a proprietary delivery device which can only be sourced from a single manufacturer. There may be a disruption or delay in the performance of our third- party contractors, suppliers or collaborators which is beyond our control. If such third parties are unable to satisfy their commitments to us, the development of our products would be adversely affected. Therefore, it is possible that our development plans will have to be slowed down or stopped completely at times due to our inability to obtain required raw materials, components, and outsourced processes at an acceptable cost, if at all, or to get a timely response from vendors, particularly as a result of recent labor market and global supply chain constraints. We have limited manufacturing capability and must rely on third- party manufacturers to manufacture our clinical supplies and commercial products, if and when approved, and if they fail to meet their obligations, the development and commercialization of our products could be adversely affected. Although we **have developed** ~~are currently in the process of further developing~~ our own internal manufacturing capabilities **which allow us to manufacture oligonucleotide drug substance for our clinical product candidates** , we **do not currently** have ~~limited~~ internal manufacturing capabilities ~~and we~~ **beyond such clinical- stage oligonucleotide drug substance. We** rely, and expect to continue to rely, on third- party manufacturers for the production of ~~some of~~ our **drug** product candidates for clinical trials and potential future commercialization. **We may choose to utilize third-party manufacturers to produce some or all of our development candidates, even if we have internal manufacturing capabilities to do so. Further, we have not developed the ability to manufacture drug product ourselves, nor have we developed the capabilities to manufacture biologics.** If we were to experience an unexpected loss or interruption of supply for any of our product candidates, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing clinical trials. Further, our drug candidates are composed of multiple components and require ~~specialized~~ **specific** formulations for which scale- up and manufacturing could be difficult. ~~We~~ **For certain products, we** have limited experience in such scale- up and manufacturing **which may** ~~requiring~~ **require** us to depend on a limited number of third parties, who may not be able to deliver in a timely manner, or at all. In order to develop products, apply for regulatory approvals, and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. **We** ~~Our internal GMP manufacturing capabilities are currently limited to small- scale production of material, although we~~ anticipate an increase in our GMP **drug substance** manufacturing capacity following the successful completion and integration of our manufacturing facility in Verona, Wisconsin. There are a limited number of manufacturers that supply synthetic oligonucleotides. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our ~~or our~~ contract manufacturers to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our development process, as well as additional expense to us. Additionally, **if** ~~our product candidates have not yet been manufactured for commercial use. If~~ any of our product candidates become approved for commercial sale, we will need to establish either internal or third- party manufacturing **and analytic** capacity. **For example, while we are still seeking regulatory approval, we intend to enter into third- party agreements for the** ~~Manufacturing~~ **manufacturing of plozasiran, in anticipation of a commercial launch in 2025. Further, some manufacturing** ~~partner~~ **partners** ~~requirements~~ may require us to fund capital improvements, perhaps on behalf of third parties, to support the scale- up of manufacturing and related activities. We may not be able to establish scaled manufacturing capacity for an approved product in a timely or economic manner, if at all. If we or our third- party manufacturers are unable to provide commercial quantities of such an approved product, we will have to successfully transfer manufacturing technology to a different **or additional** manufacturer. Engaging a new manufacturer for such an approved product could require us to conduct comparative studies or utilize other means to determine bioequivalence of the new and prior manufacturers' products, which could delay or prevent our ability to commercialize such an approved product. If we or any of these manufacturers is unable or unwilling to increase its manufacturing capacity or if we are unable to establish alternative arrangements on a timely basis or on acceptable terms, the development and commercialization of such an approved product may be delayed or there may be a shortage in supply. Any inability to manufacture our product candidates or future approved drugs in sufficient quantities when needed would seriously harm our business. While we are exploring alternative suppliers for certain critical materials, there can be no assurance that our efforts will be successful. If any of our drug candidates is approved by a regulatory authority, manufacturers of our approved products (including us, if we chose to internally manufacture) must comply with cGMP requirements relating to methods, facilities and controls used in the manufacturing, processing and packaging of the product, which are intended to ensure that drug products are safe and that they consistently meet applicable requirements and specifications. These requirements include quality control, quality assurance, and the maintenance of records and documentation. These manufacturers (including us, if we chose to internally manufacture) may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. These

requirements are enforced by the FDA and other health authorities through periodic announced and unannounced inspections of manufacturing facilities. A failure to comply with these requirements or to provide adequate and timely corrective actions in response to deficiencies identified in an inspection may result in enforcement action, including warning letters, fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, plant shutdown, or the delay, withholding, or withdrawal of product approval. If the safety of any quantities supplied is compromised due to a manufacturer' s failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products, which would seriously harm our business. We rely on independent clinical investigators, contract research organizations **(CROs)** and other third- party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We contract with certain third- parties to provide certain services, including site selection, enrollment, monitoring and data management services. We rely on these parties to carry out our clinical trials in compliance with GCP and other relevant requirements. Although we depend heavily on these parties, we do not control them and therefore we cannot be assured that these third parties will adequately perform all of their contractual obligations to us. If our third- party service providers cannot adequately and timely fulfill their obligations to us, or if the quality and accuracy of our clinical trial data is compromised due to failure by such third parties to adhere to our protocols, GCP, or other regulatory requirements or if such third parties otherwise fail to meet deadlines or quality requirements, our development plans may be delayed or terminated. Further, if clinical study results are compromised, then we may need to repeat the affected studies, which could result in significant additional costs and delays to us. Many of our competitors have greater financial resources and may have more experience in research and development, manufacturing, managing clinical trials and / or regulatory compliance than we do. Our competitors may compete with us for lead clinical trial investigators, clinical trial site locations and patient enrollment. These competitors may also compete with us on recruiting scientific and management personnel. Because our products are in various stages of preclinical and clinical development, along with many of the competing products, and given unpredictability inherent in drug development, it is difficult to predict which third parties may provide the most competition, and on what specific basis that competition may be based. Our future financial performance and our ability to commercialize products and compete effectively will depend, in part, on our ability to effectively manage future growth. We expect that as we increase the number of product candidates we are developing we will also need to expand our operations. This expected growth may place a strain on our administrative and operational infrastructure and information technology systems. As product candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing, and sales capabilities or contract with other organizations to provide these capabilities for us. We are currently ~~planning to establish~~ **establishing** a sales and marketing infrastructure, **and** although we have ~~no institutional~~ **hired individuals with significant** experience in the ~~sale~~ **sales**, marketing, or distribution of pharmaceutical products **, we have never done so as a company**. To achieve commercial success for any approved product for which we retain sales and marketing rights, we must continue to develop a sales and marketing organization or outsource these functions to third parties. If we or our collaborators are unable to establish sales, marketing and distribution capabilities or enter into or maintain agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved. Further, as our operations expand due to our development progress, we expect that we will need to manage additional relationships with various collaborators, suppliers, and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial, information technology and management controls, reporting systems and procedures. We may not be able to effectively manage the expansion of our operations or implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. Our business and operations could suffer in the event of **a cybersecurity incident or other** information technology system failures. Our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, ransomware and other cyber-attacks, human error, natural disasters, terrorism, war, and telecommunication and electrical failures. Such events could cause interruption of our operations and loss of intellectual property. For example, the loss of preclinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts and significantly increase our costs. Further, cybersecurity breaches **or other cybersecurity incidents** may allow hackers access to our preclinical compounds, strategies, discoveries, trade secrets, and / or other confidential information. Additionally, sensitive data could be leaked, disclosed, or revealed as a result of or in connection with our employees', personnel' s, vendors' or partners' use of generative AI technologies. To the extent that any disruption or ~~security~~ **cybersecurity** ~~breach~~ **incident** were to result in a loss of or damage to our data, or inappropriate disclosure of confidential, proprietary or private information, we could incur liability or regulatory penalties, including under laws and regulations governing the protection of **protected** health **information** and other ~~personally~~ -- **personal data** ~~identifiable information~~, we could lose valuable trade secret rights, the development of our product candidates could be delayed, and we could suffer reputational damage and damage to key business relationships. The risk of a ~~cyber- security~~ **cybersecurity** ~~breach~~ **incident** or other informational technology disruption, particularly through cyber- attacks, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. We **, and certain of the third parties for which we depend on to operate our business,** have experienced cyber- security attacks in the past, which to date have not had a material impact on our operations or development programs; however; there is no assurance that such impacts will not be material in the future. Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store most of these materials and various wastes resulting from their use at our facilities in Madison, Wisconsin **, Verona, Wisconsin,** and San Diego, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause interruption to our research and development and manufacturing efforts, injury to our

employees and others, environmental damage, and liabilities under federal, state and local law. In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be affected. Litigation claims may result in financial losses or harm our reputation and may divert management resources. When the market price of a stock is volatile, holders of that stock have often initiated securities class action litigation against the company that issued the stock. We cannot predict with certainty the eventual outcome of such litigation, arbitration or third- party inquiry. We may not be successful in defending ourselves or asserting our rights in current or future lawsuits, investigations, or claims that have been or may be brought against us and, as a result, our business could be materially harmed. These lawsuits, arbitrations, investigations or claims may result in large judgments or settlements against us, any of which could have a negative effect on our financial performance and business. Additionally, lawsuits, arbitrations and investigations can be expensive to defend, whether or not the lawsuit, arbitration or investigation has merit, and the defense of these actions may divert the attention of our management and other resources that would otherwise be engaged in running our business. Our operations, including any arrangements that we enter into with healthcare providers, physicians, and third- party payers, are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such laws and regulations, including applicable U. S. federal and state healthcare laws and regulations, as well as foreign laws, such as the federal Anti- Kickback Statute, the False Claims Act, the Health Insurance Portability and Accountability Act of 1996, or the Foreign Corrupt Practices Act, may constrain our operation and the business or financial arrangements through which we can market, sell and distribute any drug candidates for which we obtain marketing approval. Efforts to confirm that our business arrangements with third parties comply with applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we **may** become subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs **. We have an exclusive agreement with Vanscoy Rare Pharmacy for drug delivery services, and we expect to rely on this pharmacy for a considerable portion of our sales for plozasiran, if approved. The financial failure of Vanscoy Rare Pharmacy could adversely affect our revenues, financial condition or results of operations. Our revenues, financial condition or results of operations may also be affected by fluctuations in their buying or distribution patterns. These fluctuations may result from seasonality, pricing, wholesaler inventory objectives, or other factors** . We have incurred net losses since our inception and we expect that our operating losses will continue for the foreseeable future as we continue our drug development efforts and prepare for the potential commercialization of our product candidates. To achieve profitability, we must, either directly or through licensing and / or partnering relationships, meet certain milestones, successfully develop and obtain regulatory approval for one or more drug candidates and effectively manufacture, market and sell any drugs we successfully develop. Even if we successfully commercialize drug candidates that receive regulatory approval, we may not be able to realize revenues at a level that would allow us to achieve or sustain profitability. Accordingly, we may never generate significant revenue and, even if we do generate significant revenue, we may never achieve consistent profitability. Our business currently does not generate the cash that is necessary to finance our operations. Subject to the success of the research and development programs of our Company and our partners, and potential licensing or partnering transactions, we may need to raise additional capital to: • Fund research and development infrastructure and activities relating to the development of our drug candidates, including preclinical and clinical trials and manufacturing to support these efforts; • Fund a commercialization infrastructure and activities related to the sale, marketing, customer support, and distribution of our drug products if and when they become approved; • Fund our general and administrative infrastructure and activities; • Pursue business development opportunities for our technologies; • Add to and protect our intellectual property; and • Retain our management and technical staff. Our future capital needs depend on many factors, including: • The scope, duration, and expenditures associated with our research and development, including the progression of our clinical trials, with late- stage trials generally requiring greater capital than early- stage trials; • Regulatory requirements for our clinical trials; • The extent to which our research and development and clinical efforts are successful; • Expenditures to build out or contract for sales, marketing and distribution capabilities as we prepare for the potential commercialization of our product candidates, if any; • The outcome of potential partnering or licensing transactions, if any, and the extent to which our business development efforts result in the acquisition of new programs or technologies; • Competing technological developments; • Our intellectual property positions, if any, in our products; and • The regulatory approval process and regulatory standards for our drug candidates. We will need to raise additional funds through public or private equity offerings, debt financings or additional strategic alliances and licensing arrangements in the future to continue our operations. We may not be able to obtain additional financing on terms favorable to us, if at all. General market conditions may make it very difficult for us to seek financing from the capital markets, and the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our stockholders will result, which may substantially dilute the value of investment. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. In

order to raise additional funds through alliance, joint venture or licensing arrangements, we may be required to relinquish rights to our technologies or drug candidates or grant licenses on terms that are not favorable to us. If adequate funds are not available, we may have to further delay, reduce or eliminate one or more of our planned activities. These actions would likely reduce the market price of our common stock. **The terms of our financing agreement with Sixth Street Lending Partners and our indebtedness could adversely affect our operations and limit our ability to plan for or respond to changes in our business. If we are unable to comply with restrictions in the financing agreement, the repayment of our existing indebtedness could be accelerated. On August 7, 2024, we entered into a financing agreement with Sixth Street Lending Partners, as the administrative agent and collateral agent for several lenders. The financing agreement establishes a senior secured term loan facility of $ 500. 0 million (the " Credit Facility "), consisting of $ 400. 0 million funded on the closing date and an additional $ 100. 0 million available at the our option, subject to mutual agreement with Sixth Street, over the seven-year term. We have incurred a substantial amount of debt under the financing agreement which could adversely affect our business. The financing agreement requires us to make certain payments over time and contains several other negative covenants that, subject to certain exceptions, restrict indebtedness, liens, investments (including acquisitions), fundamental changes, asset sales and licensing transactions, dividends, modifications to material agreements, payment of subordinated indebtedness, and other matters customarily restricted in such agreements. Among other requirements of the financing agreement, we and our subsidiaries party to the financing agreement must maintain certain liquidity thresholds based on our market capitalization. We are also subject to restrictions on sales and licensing transactions with respect to our core intellectual property and product assets, including, but not limited to, olpasiran, plozasiran, zodasiran, fazirsiran, GSK4532990, and daplusiran / tomligisiran, subject to certain exceptions. These and other terms in the financing agreement could restrict our ability to grow our business or enter into transactions that we believe would be beneficial to our business. Our indebtedness could affect our business in the following ways, among other things: make it more difficult for us to satisfy our contractual and commercial commitments; require us to use a substantial portion of our cash flow subject to mandatory prepayments to pay interest and principal when due, which would reduce funds available for working capital, capital expenditures and other general corporate purposes; limit our ability to obtain additional financing for working capital, capital expenditures, acquisitions and other investments or general corporate purposes; heighten our vulnerability to downturns in our business, our industry or in the general economy; place us at a disadvantage compared to those of our competitors that may have proportionately less debt; limit management' s discretion in operating our business; and limit our flexibility in planning for, or reacting to, changes in our business, the industry in which we operate or the general economy. Our business may not generate cash flows from operations in the future that are sufficient to service our debt and support our growth strategies. In addition, our ability to generate sufficient cash flows to meet our debt obligations depends upon several factors, such as the ability of our Company and our licensees to timely complete clinical trials and obtain marketing approval for our clinical- stage product candidates, to successfully commercialize our clinical- stage product candidates, our receipt of regulatory approval for plozasiran for treatment of FCS, and our future performance, which is subject to financial, business, and other impacts on our operations, many of which are beyond our control. If we are unable to generate sufficient cash flows, we may be required to adopt one or more alternatives, such as obtaining additional equity capital on terms that may be onerous or highly dilutive, selling assets, or restructuring debt. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.** Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. Our quarterly and annual operating results have fluctuated and may continue to fluctuate significantly in the future, which makes it difficult for us to predict our future operating results. From time to time, we may enter into license or collaboration agreements or strategic partnerships with other companies that include development funding and significant upfront and milestone payments and / or royalties. These upfront and milestone payments may vary significantly from period to period and any such variance could cause a significant fluctuation in our operating results from one period to the next. In addition, we measure compensation cost for stock- based awards made to employees at the grant date of the award, based on the fair value of the award, and recognize the cost as an expense over the employee' s requisite service period. As the variables that we use as a basis for valuing these awards change over time, including our underlying stock price and stock price volatility, the magnitude of the expense that we must recognize may vary significantly. Furthermore, our operating results may fluctuate due to a variety of other factors, may of which are outside of our control and may be difficult to predict, including the following: • the timing and cost of, and level of investment in, research and development activities relating to our current and any future product candidates, which will change from time to time; • our ability to enroll patients in clinical trials and the timing of enrollment; • the cost of manufacturing our current and any future product candidates, which may vary depending on FDA guidelines and requirements, the quantity of production and the terms of our agreements with manufacturers and other suppliers; • expenditures that we will or may incur to acquire or develop additional product candidates and technologies; • the timing and outcomes of clinical trials for product candidates; • the need to conduct unanticipated clinical trials or trials that are larger or more complex than anticipated; • competition from existing and potential future products that compete with any of our product candidates, and changes in the competitive landscape of our industry, including consolidation among our competitors or partners; • any delays in regulatory review or approval of any of our product candidates; • the level of demand for any of our

product candidates, if approved, which may fluctuate significantly and be difficult to predict; • the risk / benefit profile, cost and reimbursement policies with respect to our product candidates, if approved, and existing and potential future products that compete with our product candidates; • our ability to commercialize any of our product candidates, if approved, inside and outside of the United States, either independently or working with third parties; • our ability to establish and maintain collaborations, licensing or other arrangements; • our ability to adequately support future growth; • potential unforeseen business disruptions that increase our costs or expenses; • future accounting pronouncements or changes in our accounting policies; and • the changing and volatile global economic environment. The cumulative effect of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period- to- period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated guidance we may provide. At September 30, ~~2023~~ **2024**, we had $ ~~403~~ **681**. ~~6~~ **0** million in cash, cash equivalents ~~and ,~~ restricted cash and ~~fixed income~~ **available- for- sale** securities. Our investments may also include commercial paper, securities issued by the U. S. government obligations, and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. These investments are subject to general credit, liquidity, and market and interest rate risks, particularly in the current economic environment. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition. We have historically incurred net losses. Under the Internal Revenue Code of 1986, as amended (the " Code "), a corporation is generally allowed a deduction for net operating losses (NOLs) carried forward from a prior taxable year. Under that provision, we can carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. As of September 30, ~~2023~~ **2024**, we had federal ~~and ,~~ state **, and foreign** NOL carryforwards of ~~approximately~~ $ ~~134~~ **223. 1 million, $ 693. 2 million, and $ 38**. 3 ~~million and $ 491. 5~~ million, respectively. As a result of the Coronavirus Aid, Relief, and Economic Security Act of 2020 (" CARES Act ") and legislation commonly referred to as the Tax Cuts and Jobs Act of 2017 (" 2017 Tax Act "), NOLs arising before January 1, 2018, and NOLs arising after January 1, 2018, are subject to different rules. Under the CARES Act and 2017 Tax Act, federal NOLs incurred in 2018, 2019 and 2020 can generally be carried back five years, carried forward indefinitely and can offset 100 % of future taxable income for tax years before January 1, 2021 and up to 80 % of future taxable income for tax years after December 31, 2020. Any NOLs arising on or after January 1, 2021, cannot be carried back, but can generally be carried forward indefinitely and can offset up to 80 % of future taxable income. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law. These NOL carryforwards could expire unused before offsetting potential future income tax liabilities. In addition, under Section 382 and 383 of the Code and corresponding provisions of state law, if a corporation undergoes an " ownership change, " which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three- year period, the corporation' s ability to use its pre- change NOL carryforwards and other pre- change tax attributes to offset its post- change income or taxes may be limited. It is possible that we have experienced an ownership change limitation. We may 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. If an ownership change occurs and our ability to use our NOL carryforwards is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. We could be subject to additional tax liabilities. We are subject to U. S. federal, state, and local taxes in the United States and other countries. Significant judgment is required in evaluating our tax positions. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. For instance, beginning in 2022, the 2017 Tax Act eliminated the option of expensing all research and development expenditures in the current year, instead requiring amortization over five years for expenditures in the U. S. and over fifteen years for foreign-based expenditures. There is no assurance that the requirement will be deferred, repealed, or otherwise modified. This change in law increased our tax liability for the fiscal year. We continue to monitor new tax legislation or other developments since significant changes in tax legislation, or in the interpretation of existing legislation, could materially and adversely affect our financial condition and operating results. Additionally, we may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value- added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made. Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance. Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes- Oxley Act. As a result, we continue to incur additional expenses and divert our management' s time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company

Accounting Oversight Board or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock. Our Board of Directors has the authority to issue shares of " blank check " preferred stock, which may make an acquisition of the Company by another company more difficult. We have adopted and may in the future adopt certain measures that may have the effect of delaying, deferring or preventing a takeover or other change in control of the Company that a holder of our common stock might consider in its best interest. For example, our Board of Directors, without further action by our stockholders, currently has the authority to issue up to 5, 000, 000 shares of preferred stock and to fix the rights (including voting rights), preferences and privileges of these shares (" blank check " preferred). Such preferred stock may have rights, including economic rights, senior to our common stock. These factors could also reduce the price that certain investors might be willing to pay for shares of our common stock and result in the market price being lower than it would be without these provisions. We do not intend to declare cash dividends on our common stock. We will not distribute cash to our stockholders unless and until we can develop sufficient funds from operations to meet our ongoing needs and implement our business plan. The time frame for that is unpredictable and investors should not expect dividends in the near future, if at all. The trading market for our common stock can be influenced by the research and reports that industry or securities analysts publish about our business. ~~Currently, coverage of our Company by industry and securities analysts is limited.~~ Investors have many investment opportunities and may limit their investments to companies that receive greater coverage from analysts. If additional industry or securities analysts do not commence coverage of the Company, the trading price of our stock could be negatively impacted. If one or more of the analysts downgrade our stock or comment negatively on our prospects, our stock price may decline. If one or more of these analysts cease to cover our industry or us or fail to publish reports about the Company regularly, our common stock could lose visibility in the financial markets, which could also cause our stock price or trading volume to decline. Further, incorrect judgments, estimates or assumptions made by research analysts may adversely affect our stock price, particularly if subsequent performance falls below the levels that were projected by the research analyst (s), even if we did not set or endorse such expectations. Any of these events could cause further volatility in our stock price and could result in substantial declines in the value of our stock. Although our common stock is listed for trading on the Nasdaq Global Select Market, at various times our securities are relatively thinly traded. Investor trading patterns could serve to exacerbate the volatility of the price of our stock. For example, mandatory sales of our common stock by institutional holders could be triggered if an investment in our common stock no longer satisfies their investment standards and guidelines. It may be difficult to sell shares of our common stock quickly without significantly depressing the value of the stock. Unless we are successful in developing continued investor interest in our stock, sales of our stock could result in major fluctuations in the price of the stock. Because we are still a clinical- stage pharmaceutical company and have not yet commercialized a drug, there are few objective metrics by which our progress may be measured. Consequently, we expect that the market price of our common stock will continue to fluctuate significantly. We may not continue to generate substantial revenue from the license or sale of our technology for several years, if at all. In the absence of product revenue as a measure of our operating performance, we anticipate that investors and market analysts will assess our performance by considering factors such as: • Announcements of developments related to our business; • Our ability to enter into or extend investigation phase, development phase, commercialization phase and other agreements with new and / or existing partners; • Announcements regarding the status of any or all of our collaborations or products, including clinical trial results; • Market perception and / or investor sentiment regarding our technology; • Announcements of actions taken by regulatory authorities, such as the U. S. Food and Drug Administration; • Announcements regarding developments in the RNA interference, antisense technologies, gene editing technologies or biotechnology fields in general; • Announcements regarding clinical trial results with our products or competitors' products; • Market perception and / or announcements regarding other companies developing products in the field of biotechnology generally or specifically RNA interference; • The issuance of competitive patents or disallowance or loss of our patent rights; • The addition or departure of key executives; and • Variations in our operating results. We will not have control over many of these factors but expect that they may influence our stock price. As a result, our stock price may be volatile and such volatility could result in the loss of all or part of your investment. Stockholder equity interest may be substantially diluted in any additional equity issuances. 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, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders. We 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 actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions; litigation and mass arbitration demands; fines and penalties; 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 confidential, proprietary, and sensitive information, including personal information, business data, trade secrets, intellectual property, information we collect about trial participants in connection with clinical trials, sensitive third- party data, business plans, transactions, and financial information. **These** ~~Our data processing~~ activities may subject us to numerous data privacy and security obligations **governing the collection, use, disclosure, protection, and other processing of personal data** , such as various laws, regulations, guidance, industry standards, external and internal **data** privacy and security policies, contractual requirements, and other obligations relating to data privacy and security. In the United States, there are **both** state **and federal** data privacy and security laws, including data breach notification laws, ~~personal~~ data privacy laws **(including biometric privacy laws)** , consumer protection laws (e. g., Section 5 of the Federal Trade Commission Act), **the Health Insurance**

Portability and Accountability Act (“ HIPPA **”)** , and other similar laws (e. g., wiretapping laws). For example, the California Consumer Privacy Act of 2018 **, as amended by the California Privacy Rights Act of 2020** (**together, the** “ CCPA ”) applies to personal data of consumers, business representatives, and employees, and requires businesses to provide specific disclosures in privacy notices and ~~honor requests of~~ **certain rights to** California residents **with respect** to **their personal data** ~~exercise certain privacy rights~~ . The CCPA provides for civil penalties of up to $ 7, 500 per **intentional violation and $ 2, 500 per unintentional** violation and allows private litigants affected by certain data breaches to recover significant statutory damages. ~~In addition, the California Privacy Rights Act of 2020 expands the CCPA' s requirements, including by adding a new right for individuals to correct their personal data and establishing a new regulatory agency to implement and enforce the law.~~ Outside the United States ~~,~~ **there are additional** laws, regulations, and industry standards ~~govern~~ **governing** data privacy and security. For example, the **General Data Protection Regulation (“** GDPR **”) and the GDPR as incorporated into UK law pursuant to the European Union (Withdrawal) Act 2018 (the “ UK GDPR ”)** ~~imposes~~ **impose** strict requirements for processing personal data, including health- related information. Under the GDPR **and UK GDPR** , companies may face fines of up to 20 million Euros or 4 % of annual global revenue, whichever is greater; or private litigation related to processing of personal data **. In addition, the GDPR and UK GDPR impose specific restrictions on the transfer of personal data to countries outside of the EEA and UK** . Although there are currently various mechanisms that may be used to **make such** ~~transfer~~ **transfers** ~~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, these mechanisms are subject to legal challenges. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions are subject to scrutiny from regulators, individual litigants, and activities groups. Preparing for and complying with these obligations requires us to devote resources and 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. If we or the third parties on which we rely 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 on processing personal data; and orders to destroy or not use personal data. 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; 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 substantial changes to our business model or operations. Unfavorable global economic conditions, whether brought about by material global crises, health epidemics, military conflicts or war, geopolitical and trade disputes or other factors, may adversely affect our business and financial results. Our business is sensitive to global economic conditions, which can be adversely affected by epidemics and other public health crises (such as the COVID- 19 pandemic), political and military conflict, trade and other international disputes, significant natural disasters (including as a result of climate change) or other events that disrupt macroeconomic conditions. Adverse macroeconomic conditions, including inflation, slower growth or recession, new or increased tariffs and other barriers to trade, changes to fiscal and monetary policy or government budget dynamics (particularly in the pharmaceutical and biotech areas), tighter credit, higher interest rates, volatility in financial markets, high unemployment, labor availability constraints, currency fluctuations and other challenges in the global economy have in the past adversely affected, and may in the future adversely affect, us and our business partners and suppliers. For example, trade policies and geopolitical disputes (including as a result of China- Taiwan relations) and other international conflicts can result in tariffs, sanctions and other measures that restrict international trade, and can materially adversely affect our business, particularly if these measures occur in regions where we source our components or raw materials. For example, tensions between the United States and China have led to a series of tariffs being imposed by the United States on imports from China mainland, as well as other business restrictions. Tariffs increase the costs of the components and raw materials we source. Countries may also adopt other measures, such as controls on imports or exports of goods, technology or data, that could adversely impact the Company' s operations and supply chain. These geopolitical risks could also adversely affect Visirna. Further, military conflicts or wars (such as the ongoing conflicts between Russia and Ukraine and ~~Israel and Palestine~~ **in the Middle East**) can cause exacerbated volatility and disruptions to various aspects of the global economy. The uncertain nature, magnitude, and duration of hostilities stemming from such conflicts, including the potential effects of sanctions and counter- sanctions, or retaliatory cyber- attacks on the world economy and markets, have contributed to increased market volatility and uncertainty, which could have an adverse impact on macroeconomic factors that affect our business and operations, such as worldwide supply chain issues. Additionally, the ongoing conflict between Russia and Ukraine has impacted our business decisions with respect to potential clinical trial sites in Europe. For example, a number of our clinical trial sites we had previously planned to use in Russia, Ukraine and Belarus were shut down and we had to seek alternatives in other geographies. We cannot be certain of the overall impact of the conflict between Russia and Ukraine on our ability to conduct and complete our clinical trials as planned, and any interruptions of our clinical trials can result in significant delays or termination of the research, development or commercialization of our drug candidates, which could impair our ability to generate revenues and harm our business and financial condition. Moreover, the conflict between Israel and Palestine could impact future business decisions to locate potential clinical trials in Israel. It is not possible to predict the short and long- term implications of military conflicts or wars or geopolitical tensions which could include further sanctions, uncertainty about economic and political stability, increases in inflation rate and energy prices, cyber- attacks, supply chain challenges and adverse effects on currency exchange rates and financial markets. Additionally, our operations and facilities, as well as operations of our suppliers and manufacturers, may be located in areas that are prone to earthquakes, wildfires and other natural disasters. Such operations and facilities are also subject to the risk of interruption by drought, power shortages, nuclear power plant accidents and other industrial accidents, terrorist attacks and other hostile acts, ransomware and other cybersecurity attacks, labor disputes, public health crises ~~(including the COVID- 19 pandemic)~~ , and

other events beyond the Company' s control. Global climate change is resulting in certain types of natural disasters occurring more frequently or with more intense effects. Such events can create delays or interruptions to the Company' s development efforts and inefficiencies in the Company' s supply and manufacturing chain. Significant delays in our development efforts could materially impact our ability to obtain regulatory approval and to commercialize our products. Any insurance we maintain against damage to our property and the disruption of our business due to disaster may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. Further, because the Company relies on single or limited sources for the supply and manufacture of many critical components, a business interruption affecting such sources would exacerbate any negative consequences to the Company. Any **future** public health crises ~~, including the COVID- 19 pandemic~~ , may affect our operations and those of third parties on which we rely, including our business partners and suppliers. **We** ~~In the past four years, the COVID- 19 pandemic has had an adverse impact on the global economy, including as a result of impacts associated with protective health measures that we, other businesses and governments are taking or might have to take again in the future to manage the pandemic. Without limiting the foregoing, we have experienced and / or~~ may in the future experience: • delays in receiving authorization from regulatory authorities to initiate any planned clinical trials, inspections, reviews and approvals of products; • delays or difficulties enrolling patients in our clinical trials; • delays in or disruptions to the conduct of preclinical programs and clinical trials; • constraints on the movement of products and supplies through the supply chain, which can disrupt our ability to conduct clinical trials and develop our products; • price increases in raw materials and capital equipment, as well as increasing price competition in our markets; • adverse impacts on our workforce and / or key employees; and • increased risk that counterparties to our contractual arrangements will become insolvent or otherwise unable to fulfill their contractual obligations. We are focused on technology related to new and improved pharmaceutical candidates. Product candidates that appear promising in the early phases of development, such as in animal and early human clinical trials, often fail to reach the market for a number of reasons, such as: • Clinical trial results may be unacceptable, even though preclinical trial results were promising; • Inefficacy and / or harmful side effects in humans or animals; • The necessary regulatory bodies, such as the FDA, may not approve our potential product for the intended use, or at all; and / or • Manufacturing and distribution may be uneconomical. For example, any positive preclinical results in animals may not be replicated in human clinical studies. These programs may be also found to be unsafe in humans, particularly ~~at~~ **if** higher doses **are** needed to achieve the desired levels of efficacy. Also, the positive safety results from single dose human clinical studies may not be replicated in other human studies, including multiple dose studies. Clinical and preclinical study results are frequently susceptible to varying interpretations by scientists, medical personnel, regulatory personnel, statisticians and others, which often delays, limits, or prevents further clinical development or regulatory approvals of potential products. Clinical trials can take many years to complete, including the process of study design, clinical site selection and the recruitment of patients. As a result, we can experience significant delays in completing clinical studies, which can increase the cost of developing a drug candidate and shorten the time that an approved product may be protected by patents. If our drug candidates are not successful in human clinical trials, we may be forced to curtail or abandon certain development programs. If we experience significant delays in commencing or completing our clinical studies, we could suffer from significant cost overruns, which could negatively affect our capital resources and our ability to complete these studies. **The healthcare system is under significant financial pressure to reduce costs, which could reduce payment and reimbursement rates for drugs.** Throughout the world and particularly in the United States, the healthcare system is under significant financial pressure to reduce costs. The price of pharmaceuticals has been a topic of considerable public discussion that could lead to price controls or other price- limiting strategies by payors that have the effect of lowering payment and reimbursement rates for drugs or otherwise making the commercialization of pharmaceuticals less profitable. **Many federal and state legislatures have considered, and adopted, healthcare policies intended to curb rising healthcare costs, such as the Inflation Reduction Act of 2022. These cost- containment measures may include, among other measures: requirements for pharmaceutical companies to negotiate prescription drug prices with government healthcare programs; controls on government- funded reimbursement for drugs; new or increased requirements to pay prescription drug rebates to government healthcare programs, including if drug prices increase at a higher rate than inflation; controls on healthcare providers; challenges to or limits on the pricing of drugs, including pricing controls or limits or prohibitions on reimbursement for specific products through other means; requirements to try less expensive products or generics before a more expensive branded product; and public funding for cost effectiveness research, which may be used by government and private third- party payors to make coverage and payment decisions.** Political, economic and regulatory developments may further complicate **developments in healthcare systems and pharmaceutical drug** pricing ~~negotiations, and pricing negotiations may continue after reimbursement has been obtained~~ . These ~~effects~~ **developments** could ~~reduce~~ , ~~or~~ **for** ~~eliminate~~ **example, impact our potential licensing agreements as commercial and collaborative partners may also consider the impact of these pressures on their licensing strategies. Any new laws or regulations that have the effect of imposing additional costs or regulatory burden on pharmaceutical manufacturers, or otherwise negatively affect the industry, could adversely affect** our ability to ~~return value to~~ **successfully commercialize our product candidates. The implementation of any price controls, caps on prescription drugs** ~~our~~ - **or** ~~stockholders~~ **price transparency requirements could adversely affect our business, operating results and financial condition** . Regulatory standards are promulgated by various government entities and are subject to change based on factors such as scientific developments, public perceptions of risk, and political forces. Because clinical trials often take years to complete, it is sometimes possible for standards that exist during the conception and initiation of a clinical trial to change before the clinical trial is completed or reviewed by government regulators. For example, we may initiate clinical trials that are designed to show benefits on relatively short- term endpoints, but ultimately be required to show benefits in longer- term outcome studies. While some government entities have safeguards intended to ensure standards agreed upon by sponsors and regulators at the outset of a clinical trial are applied during regulatory review processes, those safeguards generally permit

regulators to apply more rigorous standards where regulators believe doing so is necessary. As such, there can be no assurance that regulatory standards that are appropriate at the outset of a clinical trial program will not become more rigorous during the regulatory approval process and could potentially result in a delayed approval or denial of marketing authorization. ~~55~~