Risk Factors Comparison 2025-02-13 to 2024-02-15 Form: 10-K

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Investing in our securities involves a high degree of risk. You should carefully consider the following risk factors in addition to the other information set forth or incorporated by reference in this Annual Report on Form 10- K, including our consolidated financial statements and the related notes and " Management' s Discussion of Financial Condition and Results of Operations, " in evaluating our company and our business. If any of the following risks, or any additional risk not currently known to us or that we currently deem immaterial, actually occurs, our business, prospects, operating ~~result~~ **results** or financial condition could be materially and adversely affected. In these circumstances, the trading price of our common stock could decline, and you may lose all or part of your investment. SUMMARY OF MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS Our business is subject to numerous risks and uncertainties, discussed in more detail in the following section. These risks include, among others, the following key risks: Business Related Risks – Risks Related to Our Financial Results • The marketing and sale of our approved products or any future products may be unsuccessful or less successful than anticipated and we may be unable to expand the approved indications for AMVUTTRA. • We have a history of losses and may ~~never~~ **not** become and remain profitable. • We will require substantial funds to continue our research, development and commercialization activities ~~. • Any negative developments related to Leqvio could have a material adverse effect on our receipt of future royalties and milestone payments~~ . Risks Related to Our Dependence on Third Parties • We may be unable to maintain existing or enter into new collaborations with other companies that can provide business and scientific capabilities and funds for the development and commercialization of certain of our product candidates. • If any collaborator materially amends, terminates or fails to perform its obligations under agreements with us, the development and commercialization of certain of our product candidates could be delayed or terminated. • We expect to ~~continue to grow our manufacturing capabilities and resources and we must~~ incur significant costs **as we continue** to **grow our manufacturing capabilities and resources and** develop ~~this~~ **manufacturing** expertise ~~and / or~~ **; in the meantime, we** rely **, and expect to continue to rely,** on third parties to manufacture our products. • We rely on third parties to conduct our clinical trials, and if such third parties fail to fulfill their obligations, our development plans may be adversely affected. Risks Related to Managing Our Operations • If we are unable to attract and retain qualified key management and scientists, development, medical and commercial staff, consultants and advisors, our ability to implement our business plan may be adversely affected. • We may have difficulty expanding our operations successfully as we continue our evolution from a U. S.- and Europe- based company primarily involved in discovery, ~~pre- clinical~~ **preclinical** testing and clinical development into a global company that develops and commercializes multiple drugs in multiple geographies ~~including Asia, Latin America and the Middle East~~ . Industry Related Risks – Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates and the Commercialization of Our Approved Products • Any product candidate we or our collaborators develop may fail in development or ~~be~~ **experience significant** ~~delayed~~ **delays** ~~to a point where~~ **. • If any of our current or future products or product candidates causes undesirable side effects or has other unexpected adverse properties,** such ~~product candidate does not become~~ **side effects or properties could delay or prevent regulatory approval, limit the** ~~commercially~~ -- **commercial** ~~viable~~ **potential or result in significant negative consequences following any potential marketing approval** . • We or our collaborators may be unable to obtain ~~U. S. or foreign~~ regulatory approval for our or our collaborated product candidates, and, as a result, we or our collaborators may be unable to commercialize such product candidates. • Even if we or our collaborators obtain regulatory approvals, our products will be subject to ongoing regulatory oversight. • We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities with respect to our unapproved product candidates or promoting our commercially approved products in a way that violates applicable regulations. • Even if we or our collaborators receive regulatory approval to market our product candidates, the market may not be receptive to such product candidates upon their commercial introduction ~~, which could prevent us from becoming profitable~~ . • We are a multi- product commercial company and expect to continue to invest significant financial and management resources to continue to build our marketing, sales, market access and distribution capabilities and further establish our global infrastructure, and our efforts may not be successful. • Any ~~drugs~~ **products** we currently market or may develop in the future may become subject to unfavorable pricing regulations, third- party reimbursement practices or healthcare reform initiatives ~~, thereby harming our business~~ . Risks Related to Patents, Licenses and Trade Secrets • If we are not able to obtain and enforce patent protection for our discoveries, our ability to develop and commercialize our product candidates will be harmed. • We license patent rights from third- party owners. If such owners do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, our competitive position **and business, prospects, operating results and financial condition** may be harmed. • Other companies or organizations may challenge our patent rights or may assert patent rights that prevent us from developing and commercializing our products. • If we become involved in intellectual property litigation or other proceedings related to a determination of rights, including our ongoing patent infringement litigation against Pfizer, Inc., or Pfizer, and Moderna, Inc., or Moderna, we could incur substantial costs and expenses, and in the case of such litigation or proceedings against us, substantial liability for damages or be required to stop our product development and commercialization efforts. • If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing, commercializing and protecting our ~~RNAi technology~~ **current and future products and product candidates** . Risks Related to Competition • The pharmaceutical market is intensely competitive. If we or our collaborators are unable to compete effectively with existing drugs, new treatment methods and new technologies, we or our collaborators may be unable to commercialize successfully any drugs

that we or our collaborators develop. • We and our collaborators face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours, as well as from companies utilizing emerging technologies. Risks Related to Our Common Stock • Our stock price has been and may in the future be volatile, and an investment in our common stock could suffer a decline in value. • We expect that results from our and our collaborators' clinical development activities and the clinical development activities of our competitors will continue to be released periodically and may result in significant volatility in the price of our common stock. Risks Related to Our Convertible Notes • We may not have sufficient cash flow from our business to pay our indebtedness. • We may not have the ability to raise the funds necessary to settle for cash conversions of ~~the~~ **our 1 % Convertible Senior** Notes **due 2027, or the Notes,** or to repurchase the Notes for cash upon a fundamental change. • The conditional conversion feature of the Notes, if triggered, may adversely affect our liquidity. Risks Related to Our Business The marketing and sale of our approved products or any future products may be unsuccessful or less successful than anticipated, and we may be unable to expand the approved indications for certain of our commercial products, including AMVUTTRA. Although we have commercially launched four products **and have an additional product being commercialized by a collaborator** , we cannot predict whether we will successfully market and sell our approved products, or successfully expand the approved indications of certain of our commercial products, including AMVUTTRA. For example, in August and September 2022, we reported positive safety and efficacy results from the APOLLO-B Phase 3 clinical trial of patisiran, which was designed and powered to evaluate the effects of patisiran on functional capacity and quality of life in patients with ATTR amyloidosis with cardiomyopathy. ~~While we believe that the~~ **Despite positive safety and efficacy results from our** APOLLO- B ~~results after 12 months validate~~ **clinical trial, in October 2023,** the ~~therapeutic hypothesis of RNAi therapeutics targeting TTR as potential~~ **FDA issued a CRL for our sNDA for patisiran for the** treatment **of** ~~for patients with~~ ATTR amyloidosis with cardiomyopathy ~~, in October 2023, the FDA issued a CRL for our sNDA for patisiran for the treatment of ATTR amyloidosis with cardiomyopathy, indicating that the clinical meaningfulness of patisiran' s treatment effects for ATTR amyloidosis with cardiomyopathy had not been established, and therefore, the sNDA could not be approved in its submitted form~~ . To execute our business plan of building a profitable, top- tier biotech company by the end of 2025 and achieving our Alnylam P5x25 strategy and the metrics associated with such strategy, in addition to successfully marketing, selling and expanding the approved indications of our approved products, we will need to successfully: • execute product development activities and continue to leverage new technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells, including the liver, CNS, eye, lung, adipose and muscle; • build and maintain a strong intellectual property portfolio; • gain regulatory acceptance for the development and commercialization of our product candidates and successfully market our approved products, as well as any other products we commercialize; • attract and retain customers for our products; • enter into and maintain successful collaborations; and • manage our spending as **our** costs and expenses increase due to **, among other things, an increase in the number and size of our** clinical trials, ~~regulatory approvals~~ and **the expansion of our** commercialization **activities** . If we are unsuccessful in accomplishing the objectives set forth above, we may not be able to develop product candidates, successfully commercialize our approved products or any future products, raise capital, if needed, repay our indebtedness, achieve financial self- sustainability or continue our operations. We have experienced significant operating losses since our inception. As of December 31, ~~2023~~ **2024** , we had an accumulated deficit of $ 7. ~~01~~ **29** billion. Although to date we have launched four products in the U. S., EU and various other countries globally, and expect to launch our commercially approved products in additional countries during ~~2024~~ **2025** and beyond, **and have one marketed product that is commercialized by a collaborator,** we may ~~never attain~~ **not achieve or sustain** profitability or positive cash flow from operations. For the year ended December 31, ~~2023~~ **2024** , we recognized $ 1. ~~24~~ **65** billion in net product revenues from sales of ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO. **We may** ~~While we believe 2019 was our peak operating loss year, we expect to~~ continue to incur annual operating losses, and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics, and aim to achieve ~~financial self- sustainability~~ **sustainable profitability** by the end of 2025. While we believe our current cash, cash equivalents and marketable equity and debt securities, as well as the revenue we expect to generate from product sales and under our existing collaborations, including milestones and royalties on Leqvio sales, should enable us to achieve a self- sustainable profile **by the end of 2025** without the need for future equity financing, we will depend on our ability to generate product, collaboration and royalty revenues to achieve this goal. In addition to revenues derived from sales of our current and future, if any, commercially approved products, we anticipate that a portion of any revenues we generate over the next several years will continue to be from collaborations with pharmaceutical and biotechnology companies, including Roche, **Regeneron, Sanofi and** Novartis, ~~Regeneron, Sanofi~~ and **we** ~~Vir. We~~ cannot be certain that we will be able to maintain our existing collaborations, secure and maintain new collaborations, meet our obligations under collaboration agreements, or achieve any milestones that we may be required to meet or achieve to receive payments under our existing or new collaborations. Moreover, we cannot be certain that our collaborators, including **Roche and** Novartis, will continue to successfully execute their obligations under our collaboration agreements and generate collaboration and royalty revenues for us. To ~~become and~~ remain profitable, we must succeed in discovering, developing and commercializing novel product candidates with significant market potential. This will require us to build upon the success we have had in a range of challenging activities, including continued platform innovation, ~~pre- clinical~~ **preclinical** testing and clinical trial stages of development, obtaining regulatory approval and reimbursement for our novel product candidates and manufacturing, marketing and selling our approved products. We may ~~never generate revenues that are significant enough to achieve profitability and, even if we do achieve profitability, we may~~ not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot ~~become and~~ remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, develop **and commercialize** additional product candidates or continue our operations. We will require substantial funds to continue our research, development and commercialization activities, and if we require greater funds than we have estimated, we may need to critically limit,

significantly scale back or cease certain activities. We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development activities, including ~~pre- clinical~~ **preclinical** testing and clinical trials of our product candidates, and to manufacture, market and sell our ~~four~~ approved products and any other products that are approved for commercial sale. Because the length of time or scope of activities associated with successful development of our product candidates may be greater than we anticipate, we ~~are~~ **may be** unable to estimate the actual funds needed to develop and commercialize our product candidates. **Our** ~~We believe 2019 was our peak operating loss year, and believe that our current cash, cash equivalents and marketable equity and debt securities, as well as revenue we expect to generate from product sales and under our current collaborations, including milestones and royalties we expect to receive from Novartis on Leqvio sales, will enable us to achieve a self- sustainable financial profile without the need for future equity financing. Nevertheless, our~~ future capital requirements and the period for which our existing resources will support our operations may vary from what we currently expect. We have based our expectations on a number of factors, many of which are difficult to predict or are outside of our control, including: • progress in our research and development programs, including programs ~~in both rare and prevalent~~ **across a broad range of** ~~diseases~~ **disease areas and indications,** as well as what may be required by regulatory authorities to advance these programs; • the timing, receipt and amount of milestone, royalty **, research and development funding** and other payments, if any, from present and future collaborators, if any, including milestone ~~and~~ **,** royalty **and research and development funding** payments from Roche with respect to the development and commercialization of zilebesiran, as well as milestone and royalty payments from Novartis related to the commercialization of Leqvio; • our ability to **establish and** maintain **existing** and ~~establish~~ additional collaborations and / or new business initiatives; • the potential for improved product profiles to emerge from our new technologies and our ability to successfully advance our delivery efforts in extrahepatic tissues; • the resources, time and costs required to successfully initiate and complete our ~~pre-~~ **preclinical studies and** clinical **trials** ~~and clinical studies~~, obtain regulatory approvals, prepare for global commercialization of our product candidates and obtain and maintain licenses to third- party intellectual property; • our ability to establish, maintain and operate our own manufacturing facilities in a timely and cost- effective manner; • our ability to manufacture, or contract with third parties for the manufacture of, our product candidates for clinical testing and our **approved** products for commercial sale; • the impact of any future pandemics or public health emergencies or the ongoing conflicts in the Middle East and Ukraine on the initiation or completion of ~~pre- clinical~~ **preclinical** studies or clinical trials and the supply of our products or product candidates; • the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims; • the costs associated with legal activities, including litigation and government investigations, arising in the course of our business activities and our ability to prevail or reach a satisfactory result in any such legal disputes and investigations; • the timing, receipt and amount of sales milestones and royalties, if any, from our approved products and our ~~potential products~~ **product candidates** , if and when approved; and • the outcome of the regulatory review process and commercial success of **our products, including AMVUTTRA for the treatment of ATTR amyloidosis with cardiomyopathy, and** products for which we are entitled to receive royalties, including Leqvio **and fitusiran, assuming regulatory approval** . If our estimates, predictions and financial guidance relating to these factors are incorrect, we may need to modify our operating plan and may be required to seek additional funding in the future. We may do so through either collaborative arrangements, public or private equity offerings or debt financings, royalty or other monetization transactions or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all. The terms of any financing we may be required to pursue in the future may adversely affect the holdings or the rights of our stockholders. If we raise additional funds by issuing equity securities, ~~further~~ dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. If we require additional funding and are unable to obtain such funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs, or delay or curtail the further development of our global commercial infrastructure, and our ability to achieve our long- term strategic goals may be delayed or diminished. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own. Although we sold a portion of the royalty stream and commercial milestones from the global sales of Leqvio by Novartis, we are entitled to retain the remaining portions of the future royalties and commercial milestone payments on Leqvio, and any negative developments related to Leqvio could have a material adverse effect on our receipt of those payments. In April 2020, we sold to **BX Bodyguard Royalties L. P. (an affiliate of The** Blackstone **Group Inc.), or Blackstone Royalties,** 50 % of the royalties payable to us with respect to net sales by Novartis, its affiliates or sublicensees of Leqvio and 75 % of the commercial milestone payments payable to us under the MDCO **License** ~~agreement~~ **Agreement** . If Blackstone does not receive royalty payments in respect of global sales of Leqvio equaling at least $ 1. 00 billion by December 31, 2029, Blackstone **Royalties** ' ~~s~~ interest in Leqvio royalties will increase to 55 % (and our interest will decrease to 45 %) effective January 1, 2030. As a result, any factor that has an adverse impact on sales of Leqvio could affect our ability to meet the $ 1. 00 billion repayment threshold in this timeframe, which in turn would have a negative impact on the percentage of the Leqvio royalty stream that we are entitled to retain. Factors that could have an adverse impact on Leqvio sales include: • **competitors may** ~~companies working to~~ develop new therapies or alternative formulations of products for **HeFH and** ASCVD; • lack of acceptance of Leqvio by patients, the medical community or third party payors; • any negative developments relating to Leqvio, such as safety, efficacy, or reimbursement issues; • any disputes concerning patents or proprietary rights, or under license and collaboration agreements; • foreign currency exchange rate fluctuations; and • adverse regulatory or legislative developments that limit or prohibit the sale of Leqvio, such as restrictions on the use of Leqvio or safety- related label changes, including enhanced risk management programs. If the revenues generated by sales of Leqvio are lower than expected, we may not receive commercial milestone payments and / or royalties in the amount we are currently anticipating, and our business, prospects, operating results and financial condition could be materially and adversely affected.

~~Geopolitical risks associated with the ongoing military conflict between Russia and Ukraine could have an adverse impact on our business, prospects, operating results and financial condition, including our clinical trials. Russia' s invasion of Ukraine, and the global response, including the imposition of sanctions by the U. S., EU and other countries, has resulted in global business disruptions and economic volatility and may have an adverse impact on our business, including our clinical trials. The uncertain nature, magnitude, and duration of hostilities stemming from the conflict in Ukraine, including the potential effects of sanctions retaliatory cyber- attacks on the world economy and markets, have contributed to increased market volatility and uncertainty, which could continue to have an adverse impact on macroeconomic factors that might affect our business and operations. Additionally, the ongoing conflict in Ukraine has disrupted the ability of certain of our contract research organizations, or CROs, to conduct clinical trials at certain sites in Ukraine. We cannot be certain what the overall impact of this conflict will be on our ability to conduct and complete our clinical trials on schedule. However, interruptions of our clinical trials could significantly delay our clinical development plans and potential authorization or approval of our product candidates, which could increase our costs and jeopardize our ability to successfully commercialize our product candidates.~~ If the estimates we make, or the assumptions on which we rely, in preparing our financial statements and / or our projected guidance prove inaccurate, our actual results may vary from those reflected in our projections and accruals. Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. 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. Further, from time to time we issue financial guidance relating to our expectations regarding our combined product sales, collaboration and royalty revenues, and GAAP and non- GAAP combined research and development and selling, general and administrative expenses, which guidance is based on estimates and the judgment of our management. If, for any reason, our product sales, revenues and / or expenses differ materially from our guidance, we may have to adjust our publicly announced financial guidance. ~~For example, in April 2022, we decreased our 2022 guidance range for combined net product revenues, and in October 2022, we decreased our guidance range for our collaboration and royalty revenue.~~ If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline. The investment of our cash, cash equivalents and marketable securities is subject to risks which may cause losses and affect the liquidity of these investments. As of December 31, ~~2023~~ **2024** , we had $ 2. ~~44~~ **69** billion in cash, cash equivalents and marketable securities. We historically have invested these amounts in ~~high – grade corporate notes, commercial paper, securities issued or sponsored by the U. S. government, certificates of deposit and~~ money market funds ~~meeting the criteria of our investment policy~~ , **certificates** ~~which is focused on the preservation~~ of ~~our capital~~ **deposit, commercial paper, corporate notes, U. S. government- sponsored enterprise securities and U. S. treasury securities through highly rated financial institutions** . Corporate notes may also include foreign bonds denominated in U. S. dollars. These investments are subject to general credit, liquidity, market and interest rate risks. 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 financial condition. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would decline. The market risks associated with our investment portfolio may have an adverse effect on our operating results, liquidity and financial condition. Volatility in foreign currency exchange rates could have a material adverse effect on our operating results. Our revenue from outside of the U. S. is expected to increase as our products, whether commercialized by us or our collaborators, gain marketing approval in such jurisdictions. Our primary foreign currency exposure relates to movements in the Japanese yen, Euro and British pound. If the U. S. dollar weakens against a specific foreign currency, our revenues will increase, having a positive impact on net income, but our overall expenses will increase, having a negative impact. Conversely, if the U. S. dollar strengthens against a specific foreign currency, our revenues will decrease, having a negative impact on net income, but our overall expenses will decrease, having a positive impact. **Any future** ~~For example, during 2022, the dollar strengthened against certain foreign currencies, and we experienced an unfavorable impact from foreign exchange rates on our international revenues. Continued~~ volatility in foreign exchange rates is likely ~~to continue~~ to impact our operating results and financial condition. Changes in tax laws could adversely affect our business, prospects, operating results and financial condition. Our business is subject to numerous international, federal, state, and other governmental laws, rules, and regulations that may adversely affect our operating results, including, taxation and tax policy changes, tax rate changes, new tax laws, or revised tax law interpretations, which individually or in combination may cause our effective tax rate to increase. In the U. S., the rules dealing with federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U. S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, prospects, operating results and financial condition. Additionally, the Organization for Economic Co- operation and Development, or the OECD, the EC, and individual taxing jurisdictions where we and our affiliates do business have recently focused on issues related to the taxation of multinational corporations. The OECD has released its comprehensive plan to create an agreed set of international rules for fighting base erosion and profit shifting. In addition, the OECD, the EC and individual countries are examining changes to how taxing rights should be allocated among countries considering the digital economy. As a result, tax laws in the U. S. and other countries in which we and our affiliates do business could change on a prospective or retroactive basis and any such changes could materially adversely affect our business, prospects, operating results and financial condition. We may incur additional tax liabilities related to our operations. We are subject to income tax in the U. S. and the foreign jurisdictions in which we operate. Significant judgment is required in determining our worldwide tax

liabilities, and our effective tax rate is derived from the applicable statutory tax rates and relative earnings in each taxing jurisdiction. We record liabilities for uncertain tax positions that involve significant management judgment as to the application of law. Domestic or foreign taxing authorities may disagree with our interpretation of tax law as applied to our and our subsidiaries' operations or with the positions we may take with respect to particular tax issues on our tax returns. Consequently, tax assessments or judgments in excess of accrued amounts that we have estimated in preparing our financial statements may materially and adversely affect our reported effective tax rate or our cash flows. Further, other factors may adversely affect our effective tax rate, including changes in the mix of our profitability from country to country, tax effects of stock- based compensation (which depend in part on the price of our stock and, therefore, are beyond our control), and changes in tax laws or regulations. For example, the OECD Global Anti- Base Erosion Model have influenced tax laws in countries in which we operate, including the implementation of minimum taxes. Changes to these or other laws and regulations or their interpretations could materially and adversely impact our effective tax rate or cash flows. Any future outbreaks of ~~COVID- 19 and its variants, or other future~~ pandemics or public health emergencies, may directly or indirectly adversely affect our business, results of operations and financial condition. In the future, we may experience disruptions from ~~COVID- 19 or~~ a ~~future~~ pandemic or public health emergency that could impact our business and operations, including our ability to **obtain regulatory approval for and** successfully commercialize our approved products, and we may not be able to meet expectations with respect to commercial sales as a result. In addition, we may ~~also~~ experience decreased patient demand for our approved products if current or potential patients decide to delay treatment as a result of ~~the COVID- 19 or~~ a ~~future~~ pandemic or public health emergency. Business interruptions from ~~future~~ pandemics or public health emergencies, including staffing shortages, raw material or other supply chain shortages, production slowdowns and disruptions in delivery systems, may also adversely impact the third parties we or our collaborators rely on in the U. S. and abroad to sufficiently manufacture our approved products and to produce product candidates in quantities we require, which may impair our commercialization efforts, our research and development activities and the potential commercialization of our product candidates. Additionally, timely completion of ~~pre- clinical~~ **preclinical** activities and initiation of planned clinical trials are dependent upon the availability of, for example, ~~pre- clinical~~ **preclinical** and clinical trial sites, researchers and investigators, patients or healthy volunteer subjects available for recruitment and enrollment, and regulatory agency personnel, which may be adversely affected by global health matters, such as ~~the COVID- 19 pandemic or~~ any ~~future~~ pandemic or public health emergency ~~. We are conducting and plan to continue to conduct pre- clinical activities and clinical trials for our drug product candidates in geographies which have been and may again be affected by COVID- 19, and any resurgence of the COVID- 19 pandemic and its variants could have an impact on various aspects of our ongoing clinical trials and on the clinical trials and pre- clinical studies we expect to initiate during 2024~~ . Health regulatory agencies globally may also experience disruptions in their operations as a result of **a** ~~the COVID- 19~~ pandemic or future public health ~~emergencies~~ **emergency** , which could impact review, inspection and approval timelines. ~~Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume pre- pandemic levels of inspection activities, including routine surveillance, bioresearch monitoring and pre- approval inspections. Should the FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel, and the agency does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed.~~ While the ultimate impact of ~~COVID- 19, or~~ any ~~future~~ pandemic or public health emergency ~~,~~ on our business is uncertain, any negative impacts of such pandemic or public health emergency, alone or in combination with others, could exacerbate other risk factors discussed herein. The full extent to which ~~COVID- 19, or~~ any ~~future~~ pandemic or public health emergency, will negatively affect our operations, financial performance, and stock price will depend on future developments that are highly uncertain and cannot be predicted. If we are unable to maintain our existing collaborations, or enter into new collaborations with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates, it may have a negative impact on our business, prospects, operating results and financial condition. We do not currently have adequate capacity or capabilities to advance all opportunities arising from our growing pipeline of RNAi therapeutics. Accordingly, we have entered into collaborations with third party collaborators we believe can provide such capacity and capabilities in certain territories and / or for certain product candidates, and we intend to enter into additional such collaborations in the future. Specifically, we currently have active collaborations with, among others, **Roche, Regeneron,** Sanofi ~~,~~ **and** Novartis ~~, Regeneron, Vir, Novo Nordisk and Roche~~ covering various products and product candidates in our pipeline. In such collaborations, we expect our current, and may expect ~~our~~ **any** future, collaborators to provide substantial capabilities in clinical development, regulatory affairs, and / or marketing, sales and distribution. Under certain of our collaborations, we also expect our collaborators to develop, market and / or sell certain of our product candidates ~~,~~ in certain territories or globally, and we have limited or no control over the development, sales, marketing and distribution activities of these collaborators. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on (i) Regeneron for the development and commercialization of all programs targeting eye diseases (subject to limited exceptions), and potentially other CNS and liver programs; (ii) Novartis for the development and commercialization of Leqvio worldwide; (iii) Sanofi for the development and commercialization of fitusiran worldwide; and (iv) Roche for the commercialization of zilebesiran outside of the U. S. In the case of each collaboration referenced in clauses (i)- (iv) above, we are entitled to royalties, and in some instances commercial milestone payments, on the sales of the applicable product. If our collaborators are not successful in their development and / or commercialization efforts, our future revenues from the relevant product or product candidate may be adversely affected. For example, in December 2020 Novartis received a **CRL** ~~complete response letter~~ from the FDA stating that the FDA could not approve the NDA by the PDUFA action date due to unresolved inspection- related conditions at a third party manufacturing facility. While Leqvio was ultimately approved by the FDA in December 2021, the resolution of the **CRL**

~~complete response letter~~ resulted in a delay in the payment of an approval milestone and potential U. S. royalties. As discussed above, under our agreement with Blackstone **Royalties**, if the revenues generated by the royalties received by Blackstone **Royalties** from us with respect to Leqvio sales do not reach a certain level by the end of 2029, Blackstone **Royalties** will be entitled to a higher royalty percentage beginning in 2030, which would have an adverse impact on our royalty revenues beginning in 2030. We may not be successful in entering into future collaborations on terms favorable to us due to various factors, including our ability to demonstrate improved product profiles from our new technologies, ~~including our IKARIA platform,~~ our ability to successfully demonstrate proof- of- concept for our technology in humans in certain tissues or disease areas, our ability to demonstrate the safety and efficacy of our specific product candidates, our ability to manufacture or have third parties manufacture RNAi therapeutics, the strength of our intellectual property portfolio and / or concerns around challenges or potential challenges to our intellectual property portfolio. Even when we succeed in securing such new collaborations, we may not be able to maintain them **, or they may not be successful,** if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property, we are unable to secure adequate reimbursement from payors, sales of an approved drug are lower than we expected, or our collaborator changes its strategic focus **or otherwise determines not to move forward with a product or product candidate or to continue its collaboration with us**. Furthermore, any delay in entering into new collaboration agreements would have the potential to prevent or delay the development and commercialization of certain product candidates, or reduce the competitiveness such product candidates if they ultimately reach the market, which in turn could adversely affect our business, prospects, operating results and financial condition. For certain product candidates, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with **Roche,** Regeneron, ~~Roche,~~ **Sanofi and** Novartis ~~, Vir, Dicerna and Sanofi~~. We may not, however, be able to enter into additional collaborations for certain other programs, and the terms of any collaboration agreements we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of our product candidates, we may not have sufficient funds or other resources to develop these product candidates or other product candidates ~~internally~~ **on our own**, or to bring such product candidates to market. In these circumstances, we will not be able to generate revenues from these product candidates, and this will substantially harm our business, prospects, operating results and financial condition. If any collaborator materially amends, terminates or fails to perform its obligations under agreements with us, the development and commercialization of our product candidates could be delayed or terminated. Our dependence on collaborators for capabilities and funding means that our business could be adversely affected if any collaborator materially amends or terminates its collaboration agreement with us **, in whole or in part,** or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with **our** collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate. Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. In addition, our collaborators may have additional termination rights for convenience with respect to the collaboration **as a whole** or a particular program under the collaboration, under certain circumstances. For example, **in August 2024, we announced that Regeneron had opted out of further co- development and co- commercialization of mivelsiran for portfolio prioritization reasons. As a result of Regeneron' s opt- out, we have full development and commercialization rights to mivelsiran in all indications but we will be responsible for funding further development and commercialization of mivelsiran, including the ongoing Phase 2 development program, without funding from Regeneron. Regeneron will be eligible to receive low double- digit royalties on sales of mivelsiran, if approved. Our collaboration agreement with Roche requires that Roche pay us a milestone payment at the initiation of a Phase 3 clinical trial of zilebesiran. In the event that Roche determines to terminate our collaboration prior to the initiation of a Phase 3 clinical trial of zilebesiran, whether because of data from the earlier clinical development of zilebesiran** ~~our~~ **or for any other reason, we would not receive the Phase 3 milestone from Roche, which could have a material adverse effect on our operating results and financial condition and make it more difficult for us to achieve profitability in 2025. In these circumstances, we would also need to determine whether to continue the clinical development of zilebesiran in the absence of funding and other support from Roche. Our** agreement with Novartis relating to the development and commercialization of inclisiran worldwide may be terminated by Novartis at any time upon four months' prior written notice, provided if the agreement is terminated by Novartis for convenience, Novartis must grant a license to us under certain technology developed in the course of its (or MDCO' s) activities under the agreement, subject to a royalty to be negotiated between the parties. Moreover, any adverse actions by Novartis with respect to the MDCO License Agreement or disputes with Novartis regarding the MDCO License Agreement could adversely impact our ability to comply with our obligations under our agreements with Blackstone **Royalties**. If we were to lose a commercialization collaborator, we would have to attract a new collaborator (potentially on less favorable terms for us than we have with our existing collaborator) or develop expanded sales, distribution and marketing capabilities internally, which would require us to invest significant amounts of financial and management resources. In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research, development and / or commercialization of the affected product or product candidate, it could delay our development of product candidates, result in the need for additional company resources to develop **our** product candidates, require us to expend time and resources to develop expanded sales and marketing capabilities on a more expedited timeline, make it more difficult for us to attract new collaborators and ~~could~~ adversely affect how we are perceived in the business and financial communities. Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third party, the successor entity or assignee, as in the case of MDCO and Novartis, could determine that it is in its interests to: • pursue alternative technologies or develop alternative products, either on its own or jointly with

others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to ~~the~~ **its** collaboration with us; • pursue higher- priority programs or change the focus of its development programs, which could affect the collaborator' s commitment to us; or • if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us. If any of these occur, the development and commercialization of one or more products or product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own. We **expect to incur significant costs as we continue to grow our manufacturing capabilities and resources and develop manufacturing expertise; in the meantime, we rely, and expect to continue to rely, on third parties to manufacture our products and product candidates. The loss of these or future third- party suppliers, or their inability to provide us with sufficient supply, could harm our business. We** have been expanding our manufacturing capabilities, and **in order** to continue to commercialize our approved products, continue to develop our current product candidates, apply for regulatory approvals and, if approved, commercialize future products, we will need to continue to develop our internal manufacturing capabilities and / or contract or otherwise arrange for any necessary external manufacturing capabilities. ~~Historically, our internal manufacturing capabilities were limited to small- scale production of material for use in in vitro and in vivo experiments and such material was not required to be produced under current good manufacturing practice standards, or cGMP.~~ During ~~2012, we developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late- stage clinical trial use and commercial supply. In addition, during~~ 2020, we completed construction and qualification of our ~~cGMP~~ manufacturing facility in Norton, Massachusetts where we manufacture drug substances for early- stage clinical development and have the possibility to manufacture drug substances for late- stage clinical development and commercial use, in the future. At the present time, we only have the capacity to manufacture limited quantities of clinical trial drug substance ourselves, and otherwise we continue to rely on third party CMOs to manufacture additional drug substance, and we rely on third party CMOs for all of our drug product requirements for clinical and commercial use. There are a limited number of CMOs worldwide with the expertise to manufacture our siRNA therapeutic products, and we currently rely on a limited number of **CMOs in** North ~~American~~ **America** ~~and~~ **,** ~~European~~ **Europe** ~~CMOs~~ **and Asia** to manufacture our products and product candidates. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs to meet our delivery time requirements or provide adequate amounts of material to meet our needs, and if our CMOs fail to do these things it could delay our clinical trials and potentially put our commercial supply at risk, as well as result in additional expense to us. To fulfill our future requirements, we will likely need to contract with additional CMOs, and such alternative suppliers may be limited, not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner, or at all. In addition to the manufacture of synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as LNPs or conjugates or other drug delivery technologies. In some cases, the delivery technology we utilize is highly specialized or proprietary, and for technical and / or legal reasons, we may have access to only one or a limited number of potential manufacturers for such delivery technology. In addition, the scale- up of our delivery technologies could be very difficult and / or take significant time. We also have limited experience in such scale- up and manufacturing, requiring us to depend on a limited number of third parties, who might not be able to deliver in a timely manner, or at all. Failure by manufacturers to properly manufacture our delivery technology and / or formulate our siRNAs for delivery could result in unusable product, supply delays and drug shortages. Furthermore, competition for supply from our manufacturers from other companies, a breach by such manufacturers of their contractual obligations or a dispute with such manufacturers would **disrupt our clinical and / or commercial supply,** cause delays in our discovery and development efforts, ~~as well as~~ **and result in** additional expense to us. In developing manufacturing capabilities by building our own manufacturing facilities, we have incurred substantial expenditures, and expect to incur significant additional expenditures in the future. Also, we have had to, and will likely need to continue to, recruit, hire, and train qualified employees to staff our facilities. If we are unable to manufacture sufficient quantities of material or if we encounter problems with our facilities in the future, we may also need to secure alternative suppliers, and such alternative suppliers may not be available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner, or at all. Given our dependence on a limited number of CMOs to supply our commercial products and clinical candidates, and the ongoing utilization of our own facilities, any delay or setback in the manufacture of our products could impede ongoing clinical and commercial supply, which could materially and adversely impact our business, prospects, operating results ~~or~~ **and** financial condition. In addition, to the extent we or our collaborators rely on CMOs to supply our product candidates, any delays or disruptions in supply could have a material adverse impact on the research and development activities and potential commercialization of our or our collaborators' product candidates. The manufacturing processes for our products and any other product candidates that we may develop is subject to the FDA and foreign regulatory authority approval ~~process~~ **processes** and we will need to meet, and will need to contract with CMOs who can meet, all applicable FDA and foreign regulatory authority requirements on an ongoing basis. The failure of any CMO to meet required regulatory authority requirements could result in the delayed submission of regulatory applications, or delays in receiving regulatory approval for any of our or our current or future collaborators' product candidates. For example, in April 2022, due to an amendment to our vutrisiran NDA submission to address a pending inspection classification at a third- party secondary packaging and labeling facility, the FDA extended the review timeline of the NDA. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including potentially our commercial collaborators, to produce materials required for commercial supply **. Additionally, in January 2024, the U. S. House of Representatives introduced the BIOSECURE ACT (H. R. 7085), which was subsequently amended on May 15, 2024 and passed by the U. S. House of Representatives on September 9, 2024, and the Senate advanced a substantially similar bill (S. 3558), both of which would prohibit U. S. federal executive agencies from contracting with any entity where the biotechnology equipment or**

services of a " biotechnology company of concern " would be used in the performance of that contract. Generally, a " biotechnology company of concern " is a biotechnology company that is subject to the jurisdiction, direction, control, or operates on behalf of a foreign adversary' s government and poses a risk to the national security of the U. S. The final language, pathway and timing for either of these bills or their provisions to become law remain uncertain and, although the bill was passed in the House on September 9, 2024, the Senate did not pass the bill before the end of the 118th Congress' s term. Nonetheless, if these bills are re- introduced in the House and Senate and become law, or similar laws are passed, they would have the potential to severely restrict our ability to purchase services or products from, or otherwise collaborate with, certain Chinese " biotechnology companies of concern " without losing the ability to contract with, or otherwise receive reimbursement from, the U. S. government. We do business with companies in China and it is possible some of our contractual counterparties could be impacted by the legislation described above and alternative arrangements may need to be made. The new administration has substantially altered prior U. S. government international trade policy and has commenced activities to renegotiate, or potentially terminate, certain existing bilateral or multi- lateral trade agreements and treaties with foreign countries. In addition, the new administration has initiated or is considering imposing tariffs on certain foreign goods. Related to this action, certain foreign governments, including China, have instituted or are considering imposing tariffs on certain U. S. goods. It remains unclear what the new administration or foreign governments will or will not do with respect to tariffs or other international trade agreements and policies. A trade war or other governmental action related to tariffs or international trade agreements or policies has the potential to disrupt our research activities, affect our suppliers, increase the cost of materials purchased to manufacture our products, impact our ability to sell our products outside the U. S. or to sell our products outside the U. S. at competitive prices and / or to affect the U. S. or global economy or certain sectors thereof and, thus, could adversely impact our business. If the third parties we engage to supply materials or manufacture product candidates or products for preclinical testing or clinical or commercial supply should cease to do so for any reason, we would likely experience delays in advancing these preclinical tests and clinical trials and / or interruptions in commercial supply while we identify and qualify replacement suppliers or manufacturers, and we may be unable to obtain replacement supplies on terms that are favorable to us, or at all. If we are not able to obtain adequate supplies of our product candidates or products or the substances used to manufacture them, it could materially and adversely impact our business, prospects, operating results or financial condition . To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we depend, and will depend in the future, on these third parties to perform their obligations in a timely manner and consistent with contractual and regulatory requirements, including those related to quality control and quality assurance. The failure of any CMO to perform its obligations as expected, or, to the extent we manufacture all or a portion of our product candidates ourselves, our failure to execute on our manufacturing requirements, could adversely affect our business in a number of ways, including: • we or our current or future collaborators may not be able to initiate or continue clinical trials of product candidates that are under development; • we or our current or future collaborators may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates; • we may lose the cooperation of our collaborators; • our facilities and those of our CMOs, and our products could be the subject of inspections by regulatory authorities that could have a negative outcome and result in supply delays; • we may be required to cease distribution or recall some or all batches, of our products or take action to recover clinical trial material from clinical trial sites; and • ultimately, we may not be able to meet the clinical and commercial demands for our product candidates and products. We rely on independent clinical investigators, CROs, and other third- party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have contracted with, and we plan to continue to contract with, certain third parties to provide certain services **for our clinical trials** , including site selection, enrollment, monitoring, auditing and data management services. These investigators and CROs are not our employees **,** and we have limited control over the amount of time and resources they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw their time and resources away from our programs. Although we depend heavily on these parties, we control only limited aspects of their activity and therefore, we cannot be assured that these third parties will adequately perform ~~all of~~ their contractual obligations to us in compliance with regulatory and other legal requirements and our internal policies and procedures. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with applicable ~~good clinical practice, or~~ GCP ~~,~~ requirements, which are regulations and guidelines enforced by the FDA and ~~comparable~~ foreign regulatory authorities for our product candidates in clinical development, and to implement timely corrective action to address any non- compliance. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites, including in connection with the review of marketing applications. If we or any of our CROs fail to comply with applicable GCP requirements, or fail to take any such corrective action **in a timely manner or at all** , the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA, PMDA or other foreign regulatory authorities may require us to take additional action or perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority in the future, such regulatory authority will determine that any of our clinical trials comply with GCP ~~regulations~~ **requirements** . If our third- party service providers cannot adequately and timely fulfill their obligations to us for any reason, or if the quality and accuracy of our clinical trial data is compromised due to failure by ~~such~~ **a** third party service provider to adhere to our protocols or regulatory requirements or if ~~such~~ **a** third party service ~~providers~~ **provider** otherwise ~~fail~~ **fails** to meet deadlines, our development plans and / or regulatory reviews for marketing approvals may be delayed or terminated. As a result, our business, prospects, operating results and financial condition would be harmed, and our stock price would likely be negatively impacted ~~. Before conducting clinical trials to demonstrate the safety and~~

~~efficacy of our product candidates in humans in support of IND applications or similar applications in other jurisdictions, we must complete pre- clinical studies, which includes animal studies. In addition, we rely on third- party service providers to source certain materials for such pre- clinical studies. Our ability to complete our pre- clinical studies is contingent on, among other things, our ability to source animals and other supplies required for the conduct of such studies. If we are unable to obtain such supplies, we may be unable to complete such pre- clinical studies in a timely manner or at all. For example, some of our IND- enabling toxicology and other studies require certain non- human primates that have customarily been imported from the People's Republic of China and Cambodia, and the supply of these non- human primates was constrained in 2022 due to various factors. If we were to encounter delays in obtaining a sufficient supply of such non- human primates to enable the conduct of our pre- clinical studies, our ability to complete pre- clinical studies could be impaired and our submission of IND applications and similar applications in other jurisdictions could be delayed, which would have an adverse impact on the development timelines of the impacted product candidates~~ . We are highly dependent upon our senior management and our scientific, clinical, sales and medical staff. The loss of the service of any members of our senior management could significantly delay or prevent the achievement of product development and commercialization, and other business objectives, and adversely impact our stock price. Our employment arrangements with our key personnel are terminable without notice. We do not carry key person life insurance on any of our employees. We have grown our workforce significantly over the past several years and anticipate additional employee growth in the future, and we face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources to attract and reward qualified individuals than we do. **If** ~~In addition, if~~ we are not ~~successful in commercializing our approved products, we may be unable~~ -- **able** to attract and retain highly qualified sales and marketing ~~professionals~~ , **research, development,** and **other** ~~if we are not able to attract and retain qualified sales and marketing~~ professionals, it would negatively impact our ability to commercialize our approved products and any future products ~~. Accordingly, we may be unable to attract~~ and ~~retain suitably qualified individuals~~ to support our growing research, development and global commercialization efforts and initiatives, **which** ~~and our failure to do so could~~ **would** have an adverse effect on our ability to implement our future business plans. We may have difficulty expanding our operations successfully as we continue our evolution from a U. S.- and EU- based company primarily involved in discovery, ~~pre- clinical~~ **preclinical** testing and clinical development into a global company that develops and commercializes multiple products **in multiple geographies** . As we continue the commercial launches of our approved products ~~,~~ and increase the number of product candidates we are developing, we will need to continue to expand our operations in the U. S. and further develop operations in the EU and other geographies, including Asia and Latin America. To date, we have received regulatory approval for four products, which we have launched in multiple geographies globally, and we continue to expand the reach of these products with additional regulatory filings and launches. We have grown our workforce significantly over the last several years and anticipate additional employee growth globally in the future as we focus on the commercialization of our approved products ~~,~~ and achieving our Alnylam P5x25 strategy. This growth has placed a strain on our administrative and operational infrastructure and, as a result, we will need to continue to develop additional and / or new infrastructure and capabilities to support our growth and obtain additional space to conduct our global operations in the U. S., EU, Japan, Latin America and other geographies. If we are unable to develop such additional infrastructure or obtain sufficient space to accommodate our growth in a timely manner and on commercially reasonable terms, our business could be negatively impacted. As we continue the commercialization of our approved products, and as the product candidates we develop enter and advance through clinical trials, we will need to continue to expand our global development, regulatory, manufacturing, quality, compliance, and marketing and sales capabilities, or contract with other organizations to provide these capabilities for us. In addition, as our operations continue to expand, we will need to successfully manage additional relationships with various collaborators, suppliers, distributors and other organizations. Our ability to manage our operations and future growth will require us to continue to enhance our operational, financial and management controls and systems, reporting systems and infrastructure, ethics and compliance functions, and policies and procedures. We may not be able to implement enhancements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. The use of social media presents risks and challenges. **We use** ~~Social~~ **social** media ~~is being used~~ to communicate about our clinical development programs and the diseases our investigational RNAi therapeutics are being developed to treat, **including** ~~and we are utilizing what we believe is appropriate social media~~ in connection with our commercialization efforts for our approved products **. We** ~~, and we~~ intend to do the same for our future products, if approved. **While we believe our** ~~Social~~ **social media use is appropriate under current regulatory guidance, social** media practices in the biopharmaceutical industry continue to evolve and regulations and regulatory guidance relating to such use are evolving and not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us, along with the potential for litigation related to off- label marketing or other prohibited activities. For example, for our clinical- stage candidates, patients may use social media channels to comment on their experience in an ongoing blinded clinical ~~study~~ **trial** or to report an alleged adverse event, or AE. When such disclosures occur, there is a risk that ~~study~~ **trial** enrollment may be adversely impacted, **that** we **may** fail to monitor and comply with applicable AE reporting obligations or that we may not be able to defend our business in the face of the political and market pressures generated by social media due to restrictions on what we may say about our investigational products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any online platform, including a blog on the internet, or a post on a website, that can be distributed rapidly and could negatively harm our reputation. If any of these events were to occur or **if** we otherwise fail to comply with applicable regulations, we could ~~incur liability,~~ face regulatory actions or incur **liability or** other harm to our business. Our business and operations could suffer in the event of system failures or unauthorized or inappropriate use of or access to our systems. We are increasingly dependent on our information technology systems and infrastructure for our

business. We collect, store and transmit sensitive information including intellectual property, proprietary business information, including highly sensitive clinical trial data, and personal information in connection with our business operations. The secure maintenance of this information is critical to our operations and business strategy. Some of this information could be subject to ~~criminal attack or~~ **information breaches,** unauthorized access **, human error, computer viruses, denial- of- service attacks, malicious code, spam attacks, phishing, ransomware or other forms of social engineering** and ~~use~~ **other events that could impact the security, reliability, confidentiality, integrity and availability of our systems, including** by third parties with a wide range of motives and expertise, including organized criminal groups, **nation- states,** " hacktivists, " patient groups, ~~disgruntled~~ **rogue** current or former employees and others **. Cyber- attacks can be designed to collect sensitive or proprietary information, manipulate, destroy or corrupt data, systems or applications, or accounts, to steal money or extort money through the use of so- called " ransomware ", and to disable the functioning or use of applications or technology assets** . Cyber- attacks are of ever- increasing levels of sophistication, and despite our security measures, our information technology and infrastructure may be vulnerable to such attacks or may be breached, including due to employee error or malfeasance . The pervasiveness of cybersecurity incidents in..... or loss of confidential or propriety information . The risk of cyber- attacks is increased with employees working remotely ~~.~~ **, as** ~~Remote~~ **remote** work increases **our** ~~the risk we may be vulnerable~~ **vulnerability** to cybersecurity- related events such as phishing attacks and other security threats. .The pervasiveness of cybersecurity incidents in general and the risks of cyber- crime are complex and continue to evolve.Although we are making significant efforts to maintain the security and integrity of our information systems and are exploring various measures to manage the risk of a security breach or disruption,there can be no assurance that our security efforts and measures will be effective or that attempted security breaches or disruptions would not be successful or damaging.Despite the implementation of security measures,our internal computer systems and those of our contractors,consultants and collaborators are vulnerable to damage or interruption from computer viruses,unauthorized or inappropriate access or use,natural disasters,pandemics or public health emergencies,terrorism,war (including the ongoing conflicts in Ukraine and the Middle East),and telecommunication and electrical failures.Such events could cause interruption of our operations.For example,the loss of **pre-** ~~preclinical~~ --- **clinical** trial data ~~,~~ **or** data from completed or ongoing clinical trials for our product candidates ~~,or manufacturing data~~ could result in delays in our regulatory filings and development efforts,as well as delays in the commercialization of our products,and significantly increase our costs.To the extent that any disruption,security breach or unauthorized or inappropriate use or access to our systems were to result in a loss of or damage to our data,or inappropriate disclosure of confidential or proprietary information,including but not limited to patient,employee or vendor information,we could incur notification obligations to affected individuals and government agencies, ~~face~~ **liability,including** potential lawsuits from patients,collaborators,employees,stockholders or other third parties,and ~~incur~~ liability under foreign,federal and state laws that protect the privacy and security of personal information,and the development and potential commercialization of our ~~products and~~ product candidates could be delayed ~~.Such events may ultimately result in financial losses that are either not insured or are not fully covered through any insurance we maintain~~ .In addition,our increased use of cloud technologies heightens these third party **and other operational** risks,and any failure by cloud or other technology service providers to adequately safeguard their **systems and prevent cyber- attacks could disrupt our operations and result in misappropriation,corruption,or loss of confidential or propriety information** Risks Related to Our Industry **Our business depends upon** ~~Before obtaining regulatory approval for~~ the ~~commercial distribution~~ **successful development and commercialization** of our product candidates **. These** ~~, we must conduct, at our own expense, extensive nonclinical tests and clinical trials to demonstrate the safety and / or efficacy in humans of our~~ product candidates **are in various stages of development and must satisfy rigorous standards of safety and efficacy before they can be approved for sale by the FDA or foreign regulatory authorities** . Nonclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete ~~and~~ **,** is uncertain as to outcome, and the historical failure rate for product candidates is high. **It is impossible to predict when or if any of our product candidates** ~~We currently have multiple programs in clinical development, including internal and collaborated programs in Phase 3 development, as well~~ **will** ~~as several earlier- stage clinical programs~~ **prove effective and safe in humans or will receive regulatory approval** . **Failure** ~~However, we may not be able~~ to ~~further~~ advance ~~any of~~ our product candidates through clinical **development could impair our ability to ultimately commercialize products, which could materially harm our business and long- term prospects. Clinical** trials **may fail to demonstrate that our product candidates are safe for humans** and ~~regulatory approval~~ **effective for indicated uses, and earlier results, both nonclinical and clinical, may not be indicative of future clinical trial results** . ~~If we enter into~~ **Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could have a material adverse effect on our business, prospects, operating results and financial condition. Moreover, clinical data are often susceptible to varying interpretations, and many companies that have believed their product candidates performed satisfactorily in** clinical trials ~~,~~ **have nonetheless failed to obtain marketing approval of** ~~the~~ **their product candidate. For example, in June 2024, we reported positive** results from ~~nonclinical testing or early or late stage clinical trials of a product candidate may not predict the results that will be obtained in subsequent subjects or in subsequent human clinical trials of that product candidate or any other product candidate. For example, we are conducting~~ the HELIOS- B Phase 3 clinical trial of vutrisiran **for** ~~, which is investigating~~ the ~~potential~~ **treatment** of ~~vutrisiran to treat the cardiac manifestations of disease in~~ patients with ATTR amyloidosis with cardiomyopathy. While vutrisiran ~~has~~ demonstrated positive results in **the clinical trial** ~~patients with hATTR amyloidosis with polyneuropathy~~ , we cannot be certain ~~that the results from HELIOS- B will be positive or~~ that the results from HELIOS- B will support approval of vutrisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy. ~~There is a high failure rate for drugs proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving~~

promising results in earlier studies, and any such setbacks in our clinical development, including with respect to vutrisiran, could have a material adverse effect on our business, prospects, operating results and financial condition. Moreover, **certain of** our approved products and our current product candidates , employ novel delivery technologies that , with the exception of inclisiran, have yet to be extensively evaluated in human clinical trials and proven safe and effective **. In addition, from time to time, we report interim, topline, and preliminary data from our clinical trials, which is based on a preliminary analysis of then- available data, and the results and related findings and conclusions are subject to change. Interim or preliminary data from a clinical trial may not be predictive of final results from the clinical trial and are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment and treatment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. 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. If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition** . Additionally, several of our planned and ongoing clinical trials utilize an " open- label " trial design. An **In an** " open- label " clinical trial **, is one where** both the patient and investigator know whether the patient is receiving the investigational product candidate or **, if the trial includes multiple arms,** either an existing approved drug or placebo. Most typically, open- label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open- label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open- label clinical trials are aware when they are receiving treatment. Accordingly, open- label clinical trials may be subject to a " patient bias " where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open- label clinical trials may be subject to an " investigator bias " where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. The results from an open- label trial may not be predictive of future clinical trial results with any of our product candidates when studied in a blinded, controlled environment with a placebo or active control. In addition **Clinical testing is expensive** , **is difficult to design** we, the FDA or other applicable regulatory authorities, or an **and implement** institutional review board , **can take** or IRB, or similar foreign review board or committee, may **many** delay initiation of or suspend **years to complete and is uncertain as to outcome. We cannot guarantee that any** clinical trials **will be conducted as planned or completed on schedule, or at all. A failure** of a product candidate **one or more clinical trials can occur** at any time for various reasons **stage of testing, which may result from a multitude of factors** , including if we or they believe the healthy volunteer subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons , **but not limited to, flaws** adverse side effects of a product candidate or related product on healthy volunteer subjects or patients in a clinical trial **design** could result in our decision , **dose selection issues** or a decision by the FDA or foreign regulatory authority , to suspend or terminate the clinical trial, or, in the case of regulatory agencies, a refusal to approve a particular product candidate for any or all indications of use. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the availability of clinical trials for other investigational drugs for the same disease or condition, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, and the eligibility criteria for the clinical trial. We or our collaborators may experience difficulty enrolling our clinical trials due to the availability of existing approved treatments , **operational** as well as other investigational treatments in development. For example, in November 2018 we announced that due to recruitment challenges, **site implementation challenges** we had discontinued a Phase 2 study of ecmdisiran in atypical hemolytic uremic syndrome and were focusing our ecmdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment , **biostatistical plans and failure to demonstrate favorable** or difficulties retaining trial participants, including as a result of the availability of existing approved treatments or other investigational treatments or safety concerns, including the impact of pandemics or other public health emergencies, can result in increased costs, longer development times or termination of a clinical trial. Although our - **or efficacy traits** RNAi therapeutics have been generally well- tolerated in our clinical trials to date, new safety findings may emerge. The occurrence of serious adverse events, or SAEs, and / or adverse events, or AEs, can result in the suspension or termination of clinical trials of a product candidate by us, our collaborators, or the FDA or a foreign regulatory authority, and may negatively impact the clinical and / or regulatory timelines of the impacted product candidates. For example, in October 2016, we discontinued our revusiran program and in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE that occurred in a patient who was receiving fitusiran in our Phase 2 OLE study. More recently, in October 2020, Sanofi voluntarily paused dosing in all ongoing fitusiran clinical studies to assess reports of non- fatal thrombotic events in patients participating in the ATLAS Phase 3 program. Following an assessment of available data and alignment with regulators, patients restarted on fitusiran under amended protocols in ongoing clinical studies and, in October 2021, Sanofi announced that a potential filing date for fitusiran had been moved to 2024 due to the introduction of a revised dosing regimen in the ongoing phase 3 studies. In addition, the occurrence of SAEs and / or AEs could also result in refusal by the FDA or a foreign regulatory authority to approve a particular product candidate for any or all indications of use, or in limitations in the label of any approved product. Clinical trials also require the review, oversight and approval of IRBs, or, outside of the U. S., independent ethics committees, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB or ethics committee approval can

~~prevent or delay the initiation and completion of clinical trials, and the FDA or foreign regulatory authorities may decide not to consider any data or information derived from a clinical trial not subject to initial and continuing IRB or ethics committee review and approval, as the case may be, in support of a marketing application. Our product candidates that may encounter problems during clinical trials that will cause us, an IRB, ethics committee or regulatory authorities to delay, suspend or terminate these clinical trials, or that will delay or confound the analysis of data from these clinical trials~~. If our product candidates experience any such problems, we may not have the financial resources necessary to continue development of the affected product candidate or any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate or any of our other product candidates. A failure of one or more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, nonclinical testing and the clinical trial process that could extend our clinical development timelines and delay or prevent regulatory approval or our ability to commercialize our product candidates, including: • our nonclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional nonclinical testing or clinical trials, or we may abandon projects that have the potential to be promising; • delays in filing IND applications or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs / ethics committees in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced; • conditions imposed on us by an IRB or ethics committee, or the FDA or comparable foreign regulatory authorities regarding the scope or design of our clinical trials; • problems in engaging IRBs or ethics committees to oversee clinical trials or problems in obtaining or maintaining IRB or ethics committee approval of clinical trials; • delays in enrolling patients and volunteers into clinical trials, and variability in the number and types of patients and volunteers available for clinical trials, including as a result of ~~the COVID- 19 pandemic,~~ a ~~future~~ pandemic or public health emergency ~~and~~ **or** the ongoing ~~conflict~~ **conflicts** in Ukraine **and the Middle East** ; • disruptions caused by man- made or natural disasters or pandemics, epidemics or public health emergencies or other business interruptions; • high drop- out rates for patients and volunteers in clinical trials; • negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours; • inadequate supply or quality of product candidate materials or other materials necessary for the conduct of our clinical trials or disruption or delays in clinical supply due to ~~the COVID- 19 or~~ a future pandemic or public health emergency ~~; • greater than anticipated clinical trial costs~~ ; • serious and unexpected drug- related side effects experienced by patients taking our approved products, participants in our clinical trials or individuals using drugs similar to our products or product candidates; • poor or disappointing effectiveness of our product candidates during clinical trials; • **the imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or manufacturing concerns or after an inspection of our clinical trial operations or trial sites; •** unfavorable FDA or other regulatory agency inspection and review of a clinical trial site or records of any clinical or nonclinical investigation; • failure of our third- party contractors or investigators to comply with regulatory requirements, including **GLP,** GCP and cGMP, or otherwise meet their contractual obligations in a timely manner, or at all; • governmental or regulatory delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; ~~or~~ **• delays in reaching a consensus with regulatory agencies on trial design;** • interpretations of data by the FDA and similar foreign regulatory agencies that differ from ours **; • lack of adequate funding to continue the clinical trial; or • diminished revenue potential of the applicable program due to competition. Clinical trials must be conducted in accordance with the legal requirements, regulations or guidelines of the FDA and corresponding regulatory authorities outside the United States. We could encounter delays if a clinical trial is suspended or terminated by us, by the FDA or any other regulatory authority, or if the IRBs of the institutions in which such trials are being conducted suspend or terminate the participation of their clinical investigators and sites subject to their review. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Difficulty in enrolling patients could delay or prevent clinical trials of our product candidates, and ultimately delay or prevent regulatory approval. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Our ability to enroll patients in our clinical trials in sufficient numbers and on a timely basis is subject to a number of factors. Clinical trials are expensive and require significant operational resources. Delays in patient enrollment or unforeseen drop- out rates may result in increased costs and longer development times. Patient enrollment is affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the availability of clinical trials for other investigational drugs for the same disease or condition, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, the eligibility criteria for the clinical trial, the risk that patients enrolled in clinical trials will drop out of the clinical trials before clinical trial completion, and factors we may not be able to control, such as potential pandemics. We or our collaborators may experience difficulty enrolling our clinical trials due to the availability of existing approved treatments, as well as other investigational treatments in development. For example, we may experience delays in recruiting and enrolling patients, and in particular treatment- naive patients, for our planned Phase 3 clinical trial of nucresiran for the treatment of ATTR amyloidosis with cardiomyopathy because there are multiple approved therapies on the market for that indication. Delays or difficulties in patient enrollment, or difficulties retaining trial participants, including as a result of the availability of existing approved treatments or other investigational treatments, safety**

concerns, or the impact of pandemics or other public health emergencies, can result in increased costs, longer development times or termination of a clinical trial. Although our RNAi therapeutics have been generally well- tolerated in our clinical trials to date, new safety findings may emerge. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. There can be no assurance that our product candidates will not cause undesirable side effects. If any product candidates we develop are associated with unacceptable side effects or deaths, we may need to abandon the development of such product candidates or limit development to certain uses or subpopulations in which the unacceptable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective, any of which would have a material adverse effect on our business, financial condition, results of operations and prospects. Furthermore, the occurrence of such adverse events could result in the suspension or termination of clinical trials of a product candidate by us, our collaborators, IRBs or ethics committees, or the FDA or a foreign regulatory authority, and may negatively impact the clinical and / or regulatory timelines of the impacted product candidates. For example, our Phase 1 clinical trial of mivelsiran for Alzheimer' s Disease remains on partial clinical hold in the United States due to findings observed in non-clinical chronic toxicology studies. While our clinical development of mivelsiran has not been impacted by the partial clinical hold because of the dose levels at which it applies, it is possible that the partial clinical hold could have an impact if our development plans change or that future partial or full clinical holds on mivelsiran or our other product candidates could impact our ability to advance the clinical development of such product candidate on our expected timelines or at all. In addition, the occurrence of serious adverse events could also result in refusal by the FDA or a foreign regulatory authority to approve a particular product candidate for any or all indications of use, or in limitations in the label of any approved product . Even if we ~~successfully complete clinical trials~~ **are able to demonstrate that any future serious adverse events are not product- related and regulatory authorities do not order us to cease further development** of our product candidates, **such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate** any ~~given~~ **clinical trial of any** product candidate **, the commercial prospects of such product candidates** may ~~not prove to~~ be **harmed** ~~a safe~~ and ~~effective treatment~~ **our ability to generate product revenues from any of these product candidates may be delayed** ~~for~~ **or eliminated. Any of** ~~the~~ **these** ~~disease for which it was being tested~~ **occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly** . We or our collaborators may be unable to obtain U. S. or foreign regulatory approval for our or our collaborated product candidates and, as a result, we or our collaborators may be unable to commercialize such product candidates. **Any** ~~Our and our collaborated~~ product candidates **we or our collaborators develop** are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, pricing, **advertising, promotion and distribution of drugs. Failure to obtain** marketing ~~and distribution of drugs~~ **approval for a product candidate we may develop will prevent us from commercializing the product candidate in a given jurisdiction** . **Securing** ~~Rigorous nonclinical testing and clinical trials and an extensive~~ regulatory approval **requires the submission of extensive nonclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing** process ~~are required~~ to **,** ~~be successfully completed in the U. S.~~ and **inspection of manufacturing facilities by, the relevant regulatory authorities** ~~in many foreign jurisdictions before a new drug can be marketed~~ . Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that the product candidates we and our collaborators are developing will not obtain the regulatory approvals necessary for us or our collaborators to begin selling them, or, in the case of vutrisiran, will not obtain regulatory approval to be sold for ~~a~~ **an additional,** broader indication than the indication for which it is currently approved. It is also possible that the FDA or other regulatory authorities may determine that the data generated in clinical trials for a product candidate is not sufficient to support the approval of an application for regulatory approval. For example, although we reported positive results from the APOLLO- B Phase 3 ~~study~~ **clinical trial** of patisiran in patients with ~~ATTR amyloidosis with cardiomyopathy, and received a 9: 3 vote from the FDA' s CRDAC that patisiran' s benefits outweighed its risks for the treatment of~~ ATTR amyloidosis with cardiomyopathy, in October 2023, the FDA issued a CRL in response to our sNDA for patisiran, indicating the sNDA could not be approved in its present form. The time required to obtain FDA and other regulatory approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are not always applied in a predictable or uniform manner and can change over time. Any analysis we perform of data from nonclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We or our collaborators may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be. Because ~~the product candidates we or our collaborators are developing represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we or our collaborators may submit. Moreover, the FDA may respond to these submissions by defining requirements we or our collaborators may not have anticipated. Such responses could lead to significant delays and increased costs in the development of our or our collaborated product candidates. In addition, because~~ there may be approved treatments for some of the diseases for which we or our collaborators may seek approval, including

vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy, or treatments in development which ~~are~~ **will be** approved by the time we or our collaborators file for approval, in order to receive regulatory approval, we or they may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases are not only safe and effective, but safer and / or more effective than **other** ~~existing approved~~ products. Interruption or delays in the operations of the FDA, EMA and comparable foreign regulatory agencies may impact the review, inspection and approval timelines for our or our collaborated product candidates. During the COVID- 19 public health emergency, the FDA worked to ensure timely reviews of applications for medical products in line with its user fee performance goals and conducted mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. In addition, during the COVID- 19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA' s inability to complete required inspections for their applications. In December 2020, the FDA issued a CRL regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection- related conditions. In July 2021, Novartis announced that the resubmission to the FDA of the inclisiran NDA to address the complete response letter was filed, and the FDA approved Leqvio (the trade name under which inclisiran is marketed in the U. S.) in December 2021. This delay in the approval of Leqvio resulted in delayed milestone and royalty revenue to us. Any similar interruption or delay by the FDA, EMA or comparable foreign regulatory authorities could have a material adverse effect on our or our collaborators' efforts to obtain regulatory approval for our or our collaborators' product candidates, which could have a material adverse effect on our business, prospects, operating results or financial condition. **Inadequate funding for the FDA and other government agencies and / or potentially shifting priorities under the new administration could hinder the FDA' s and / or those other government agencies' ability to hire and retain key leadership and other personnel, prevent new products and services from being developed and / or commercialized in a timely manner, or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business. The ability of the FDA to review and approve new products, to provide feedback on clinical trials and development programs, to meet with sponsors and to otherwise review regulatory submissions can be affected by a variety of factors, including government budget and funding levels; the ability to hire and retain key personnel and accept the payment of user fees; and statutory, regulatory, and policy changes, among other factors. Average review times at the agency may fluctuate as a result. Delays at the FDA as a result of these or other factors could impact the FDA' s ability to act on our sNDA submission for vutrisiran by the PDUFA target action date of March 23, 2025, or our other regulatory submissions, including our collaborator Sanofi' s NDA for fitusiran. In addition, government funding of other government agencies or of government programs that provide research funding on which our operations may rely directly or indirectly via third party research and development projects associated with our product development programs, is subject to the political process, which is inherently fluid and unpredictable. The failure for such funding to be furnished or to be furnished in a timely manner could impact our ongoing research and development initiatives. Any disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and / or approved by necessary government agencies or to otherwise respond to regulatory submissions which would adversely affect our business.** For ~~instance~~ **example** , **the new administration has discussed several changes to the reach and oversight of** the FDA **, which could affect its relationship with the pharmaceutical industry, transparency in decision making and ultimately the cost and availability of prescription drugs. Additionally, over the last several years, the U. S. government has shut down multiple times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA and other government employees and stop critical activities. For example, the new administration recently announced plans to reduce the number of federal employees by establishing voluntary termination programs, by position eliminations or by involuntary terminations. If funding for the FDA is reduced, if the FDA workforce is reduced, if FDA priorities are changed or if a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, including our pending sNDA submission for vutrisiran and our collaborator Sanofi' s pending NDA for fitusiran, which could have a material adverse effect on our business. The FDA or foreign regulatory authorities** may request additional clinical or other data or information in connection with the regulatory review of our or our collaborators' product candidates, including by issuing a complete response letter ~~which~~ **that** may require that we or our collaborators submit additional clinical or other data or impose other conditions that must be met in order to secure final approval of our or our collaborators' NDA applications, including potentially requiring a facility inspection. Even if such data and information are submitted, or any such inspection is completed, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval **. We may seek a Fast Track, Priority Review, or Breakthrough Therapy designation or similar designations outside the U. S. for some of our product candidates. Product candidates that receive one or more of these designations may be eligible for, among other things, a priority regulatory review. Each of these designations is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for Fast Track, Priority Review, and / or Breakthrough Therapy designation, the FDA or similar regulatory authorities may disagree and instead determine not to make such designation. The receipt of one or more of these designations for a product candidate does not guarantee a faster development process, review or approval compared to products developed or considered for approval under conventional assessment procedures and does not assure ultimate approval by the FDA or similar regulatory authorities. In addition, even if one or more of our products or product candidates qualifies for Fast Track, Priority Review, and / or Breakthrough Therapy designation, the FDA or similar regulatory authorities may later decide to withdraw such designation if it determines that the product or product candidate no longer meets the conditions for qualification** . Any delay or failure in obtaining required approvals for our product candidates or our collaborated product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we or our collaborators may

seek approval in the future. For example, as a result of the ~~recent~~ CRL from the FDA in response to our sNDA for patisiran as a treatment for ATTR amyloidosis with cardiomyopathy, our ability to generate product revenues for patisiran ~~will be~~ **has been** negatively impacted. Furthermore, **even if we or our collaborators receive approval of** ~~any~~ **an NDA or foreign marketing application for a product candidate, the FDA or the applicable foreign** regulatory **agency may grant** approval ~~to~~ **or other marketing authorization contingent on the performance of costly additional clinical trials, including post-** market ~~any~~ **clinical trials. The FDA or the applicable foreign regulatory agency also may approve or authorize for marketing a** product **candidate** ~~may be subject to limitations on the approved uses~~ for ~~which we or~~ **a more limited indication** ~~our~~ **or** ~~collaborators may market~~ **patient population than we originally request, and** the **FDA or applicable foreign regulatory agency may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a** product ~~or~~ **candidate. Any of** ~~the~~ **these** ~~labeling or other~~ restrictions ~~, which~~ **or commitment** could limit ~~each such~~ **an approved** product' s market opportunity and have a negative impact on our business, prospects, operating results and financial condition and our stock price. **For example, if the FDA or foreign regulatory agency approves the sNDA for vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy with a more limited label than we are seeking, it could limit the scope of the commercial opportunity for vutrisiran.** In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, ~~plan~~ as part of its review of an NDA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe- use criteria and requiring treated patients to enroll in a registry. In the EU, we or our collaborators could be required to adopt a similar plan, known as a risk management plan, and our products could be subject to specific risk minimization measures, such as restrictions on prescription and supply, the conduct of post- marketing safety or efficacy studies, or the distribution of patient and / or prescriber educational materials. In either instance, these limitations and restrictions may limit the size of the market for our products and affect reimbursement by third- party payors. We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third- party reimbursement. The foreign regulatory approval process varies among countries and includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not ensure approval by any regulatory authority outside the U. S. and vice versa. **Our** ~~Even if we or our collaborators obtain regulatory approvals, our~~ marketed products ~~will be~~ **and any product candidates for which we obtain approval are** subject to **extensive and** ongoing regulatory oversight. If we or our collaborators fail to comply with continuing U. S. and foreign requirements, our approvals could be limited or withdrawn, we could be subject to other penalties, and in any such case our business would be seriously harmed. ~~Following~~ **Our five marketed products, including one product that is commercialized by a collaborator, and** any ~~initial~~ **product candidates for which we or our collaborators may ultimately receive marketing authorization, subject to ongoing** regulatory **requirements governing the testing, manufacturing, labeling, packaging, storage, advertising, promotion, sale, distribution, import, export, recordkeeping, and reporting. Ongoing FDA requirements include, among other things, submission of safety and other post- marketing information and reports, registration and listing, continued compliance with GMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians, and GCP requirements for any clinical trials that we conduct post-** approval ~~of a~~ **. In addition, we are conducting, and intend to continue to conduct, clinical trials for our** product **candidates** ~~we or our collaborators may develop~~ , ~~including our~~ **and we intend to seek approval to market** ~~four~~ **our** ~~approved products~~ **product candidates** , ~~we~~ **in jurisdictions outside of the U. S., and therefore** will be subject to **, and must comply with, regulatory requirements in those jurisdictions. Our products are subject to** continuing regulatory oversight **following approval** , including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This includes results from any post- marketing tests or surveillance to monitor the safety and efficacy of our approved products or other products required as a condition of approval or otherwise agreed to by us. ~~The regulatory~~ **Products are more widely used by patients once** ~~approvals~~ **approval has been obtained and therefore side effects and other problems may be observed after approval** that ~~we receive~~ **were not seen** ~~for~~ **or** ~~ONPATTRO~~ **anticipated** , **or were not** ~~AMVUTTRA, GIVLAARI and OXLUMO,~~ as **prevalent** ~~well as any regulatory approvals we receive for~~ **or severe** ~~any of our product candidates may also be subject to limitations on the approved uses for which the product may be marketed~~ , **during pre** ~~including any expanded label for AMVUTTRA. Other ongoing regulatory requirements include, among other things, submissions of safety and other post~~ **approval** ~~marketing information and reports, registration and listing, as well as continued compliance with good practice quality guidelines and regulations, including cGMP requirements and GCP requirements for any~~ clinical trials **or** ~~that we conduct post- approval. In addition, we are conducting, and intend to continue to conduct, clinical~~ **nonclinical studies** ~~trials for our product candidates, and we intend to seek approval to market our product candidates, in jurisdictions outside of the U. S., and therefore will be subject to, and must comply with, regulatory requirements in those jurisdictions~~ . The **subsequent discovery** ~~FDA has significant post- market authority, including, for example, the authority to require labeling changes based on new safety information and to require post- market studies or clinical trials to evaluate serious safety risks related to the use~~ of ~~a product and to require withdrawal of the product from the market. The FDA also has the authority to require a REMS plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved product. As our approved products are used commercially, we or others could identify~~ previously unknown ~~side effects~~ or ~~known side effects~~ **underestimated problems with a product** could **result** ~~be observed as being more frequent or severe than~~ in ~~clinical studies or earlier post- marketing periods, in which case~~ : • sales of our approved products may be lower than originally anticipated; • regulatory approvals for our approved products may be restricted or withdrawn; • we may decide, or be required, to send product warning letters or field alerts to physicians, pharmacists and hospitals; • additional

nonclinical **studies** or clinical ~~studies~~ **trials**, changes in labeling, adoption of a REMS plan, or changes to manufacturing processes, specifications and / or facilities may be required; and / or • government investigations or lawsuits, including class action suits, may be brought against us. Any of the above occurrences could reduce or eliminate sales of our approved products, increase our expenses and impair our ability to successfully commercialize one or more of these products. The CMO and manufacturing facilities we use to make our approved products and certain of our current product candidates, including our Cambridge facility, our Norton facility, as well as facilities at Agilent and other CMOs, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. For example, Agilent and our Cambridge- based facility were subject to regulatory inspection by the FDA and the EMA in connection with the review of our applications for regulatory approval for ONPATTRO and GIVLAARI, and may be subject to similar inspection in connection with any subsequent applications for regulatory approval of one or more of our products filed in other territories. The discovery of any new or previously unknown problems with our or our CMO' s manufacturing processes or facilities, may result in restrictions on the ~~drug or~~ CMO or **facility or the products manufactured at such** facility, including delay in approval or ~~, in the future,~~ withdrawal of ~~the~~ **an approved** product from the market. For example, due to a routine inspection by the FDA at a CMO facility that resulted in a pending inspection classification, we amended our regulatory submission for vutrisiran **for the treatment of hATTR- amyloidosis with polyneuropathy in adults**, which delayed our PDUFA goal date and AMVUTTRA' s FDA approval. **We** ~~Although we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use and in 2020 completed construction of a cGMP manufacturing facility for drug substance for clinical and, eventually, commercial use, we~~ may not have the ability or capacity to manufacture material at a broader commercial scale in the future. We may manufacture clinical trial materials, or we may contract a third party to manufacture this material for us. Reliance on CMOs entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the applicable CMO for regulatory compliance. If we or our collaborators, CMOs or service providers fail to comply with applicable continuing regulatory requirements in the U. S. or **a** foreign ~~jurisdictions~~ **jurisdiction** in which we seek to market our products, we or they may be subject to, among other things, fines, warning **or untitled** letters, holds on clinical trials, refusal by the FDA or foreign regulatory authorities to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, **fines,** ~~injunction~~ **injunctions**, civil penalties and criminal prosecution. ~~Physicians~~ **Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our approved products and any product candidates we may develop and adversely affect our business, financial condition, results of operations and prospects. The U. S. Supreme Court' s June 2024 decision in Loper Bright Enterprises v. Raimondo overturned the longstanding Chevron doctrine, under which courts were required to give deference to regulatory agencies' reasonable interpretations of ambiguous federal statutes. The Loper decision could result in additional legal challenges to regulations and guidance issued by federal agencies, including the FDA, on which we rely. Any such legal challenges, if successful, could** have **a material impact on our business. Additionally, the Loper decision may result in increased regulatory uncertainty, inconsistent judicial interpretations, and other impacts to the agency rule- making process, any of which could adversely impact our business and operations. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action or as a result of legal challenges, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, our business could be materially harmed. The FDA and other regulatory agencies closely regulate the post- approval marketing and promotion of products to ensure that** ~~the~~ **they** ~~discretion~~ **are marketed only for the approved indications and in accordance with the provisions of the approved labeling. Although physicians are generally permitted, based on their medical judgment,** to prescribe ~~approved drug~~ products for **indications** ~~uses that are not described in the~~ **other** ~~product' s labeling and that~~ **than** ~~differ from~~ those approved by the ~~FDA or other~~ applicable regulatory ~~agencies. Off~~ **agency, manufacturers are prohibited from promoting their products for such off** - label uses ~~are common across medical specialties~~. ~~Although~~ **For example, we may not currently promote ONPATTRO or AMVUTTRA in** the ~~FDA and~~ **U. S. for use in any indications** other **than the treatment of hATTR amyloidosis with polyneuropathy in adults. If a** regulatory ~~agencies~~ **agency determines** that ~~approve drug products do not regulate a physician' s practice of medicine or~~ **our promotional materials** ~~choice of treatments~~, **or** ~~the FDA and~~ other **activities constitute off- label promotion, it could request that we modify our promotional materials or other activities, conduct corrective advertising, or subject us to** regulatory ~~agencies regulate~~ **enforcement actions, such as the issuance of** a ~~manufacturer' s communications regarding~~ **warning or untitled letter, injunction, seizure, civil fines and criminal penalties. It also is possible that other federal, state, or foreign enforcement authorities might take action if they believe that the alleged improper promotion led to the submission and payment of claims for an** off- label use ~~and prohibit off- label promotion~~, **which could result in significant fines or penalties under other statutory authorities, such** as **laws prohibiting** ~~well as the dissemination of~~ false **claims** ~~or~~ **for reimbursement** ~~misleading labeling or promotional materials, including by their agents~~. ~~Manufacturers and their agents may~~ **Even if it is later determined we were** not **in violation** ~~promote drugs for off~~ - **of** ~~- label uses or provide information in the~~ **these laws, we may be faced** ~~promotion of drug products that is not consistent~~ with **negative publicity** ~~the approved labeling for those products. For example~~, **incur significant expenses defending** ~~we may not currently promote ONPATTRO or~~ **our actions** ~~AMVUTTRA in the U. S. for use in any indications other than the treatment of hATTR amyloidosis with polyneuropathy in adults. The FDA and other regulatory and enforcement authorities actively enforce laws and regulations prohibiting promotion of off- label uses and the promotion of products for which marketing approval has not been obtained~~, and ~~if in the future we are found to~~ have ~~improperly marketed or promoted any of our commercial products, we may be subject~~ to ~~a broad range of civil, administrative~~

~~and criminal penalties, including injunctive relief related to such commercial products' promotional activities, substantial fines or penalties, and other legal or equitable sanctions. Any adverse decision, finding, allegation, or exercise of enforcement or regulatory discretion could harm our business, prospects, operating results, and financial condition. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence. Notwithstanding regulations related to product promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non- misleading and non- promotional scientific exchange concerning their products, and we intend to engage in medical education activities and communicate with healthcare providers in compliance with all applicable laws and regulatory guidance. Nonetheless, the FDA, other applicable regulatory authorities, competitors, and other third parties may take the position that we are not in compliance with such regulations, and if such non- compliance is proven, it could harm our reputation or~~ divert **significant** ~~financial and~~ management resources from ~~our core business, and would have a material adverse effect on our business, prospects, operating results or financial condition. Moreover, any threatened or actual government enforcement actions or lawsuits by third parties could also generate adverse publicity, which could decrease demand for our products and require that we devote substantial resources that otherwise could be used productively on~~ other **matters** ~~aspects of our business. In addition to our medical education efforts, we also offer patient support services to assist patients receiving treatment with our commercially approved products. Manufacturers have increasingly become the focus of government investigation of patient support programs based on allegations that through such services illegal inducements are provided to physicians and / or patients, leading to improper utilization of government resources through Medicare, Medicaid and other government programs. Companies that are found to have violated laws such as the federal Anti- Kickback Statute and / or the federal False Claims Act, or FCA, face significant liability, including civil and administrative penalties, criminal sanctions, and potential exclusion from participation in government programs. As described below, we remain focused on our global compliance program, which is designed to support the execution of these programs and activities in compliance with applicable laws~~ . Even if we or our collaborators receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which could adversely affect our business, prospects, operating results and financial condition. **It may be difficult** ~~The product candidates that we are developing are based upon new technologies or~~ **for us to convince the medical community and** ~~therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians,~~ third- party payors ~~and consumers, may not accept a product intended to improve therapeutic results based on RNAi technology. As a result, it may be more difficult for us to convince the medical community and third- party payors~~ to accept and use our products, or to provide favorable reimbursement. ~~Other~~ **The** factors we believe will materially affect market acceptance of our products include: • the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained; • the safety and efficacy of our product candidates, as demonstrated in clinical trials and as compared with alternative treatments, if any; • relative convenience, dosing regimen and ease of administration of our product candidates; • the willingness of patients to accept potentially new routes of administration or new or different therapeutic approaches and mechanisms of action; • the success of our physician education programs; • the availability of adequate government and third- party payor reimbursement; • the pricing of our products, particularly as compared to alternative treatments, and the market perception of such prices and any price increase that we may implement in the future; and • availability of alternative effective treatments for the diseases that our product candidates we develop are intended to treat and the relative risks, benefits and costs of those treatments. For example, ONPATTRO utilizes an intravenous mode of administration with pre- medication that physicians and / or patients may not readily adopt, and which may not compete favorably with other available options for the treatment of hATTR amyloidosis with polyneuropathy in adults, including ~~inotersen~~ **WAINUA (eplontersen)** , **which is** marketed by **AstraZeneca and** Ionis ~~in several countries~~ **, and administered subcutaneously, or tafamidis** , which is ~~administered subcutaneously, or tafamidis,~~ marketed by Pfizer in several countries **and administered** ~~, which is~~ in pill form. In addition, fitusiran represents a new approach to treating hemophilia **,** which may not be readily accepted by physicians and patients and their caregivers. ~~Assuming positive results from the HELIOS- B Phase 3 clinical trial, vutrisiran~~ **Vutrisiran** , if approved for the treatment of ATTR amyloidosis with cardiomyopathy, **is administered through a subcutaneous injection and** could face similar challenges in market acceptance. We are a multi- product commercial company and expect to continue to invest significant financial and management resources to continue to build our marketing, sales, market access and distribution capabilities and further establish our global infrastructure. If we are not able to continue to develop and scale these capabilities, we may not be able to successfully commercialize our ~~current and any future~~ products **and product candidates** . We received our first product approval in August 2018 and have established capabilities for marketing, sales, market access and distribution over the last several years. We currently expect to rely on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we are commercializing ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, and intend to commercialize other product candidates, if approved, on our own globally in major markets. Accordingly, we have developed internal marketing, sales, market access and distribution capabilities as part of our core product strategy initially in the U. S., Europe and Japan, with expansion ongoing globally, which has required, and will continue to require, significant financial and management resources. For those products for which we will perform marketing, sales, market access and distribution functions ourselves ~~, including ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, and for future products we successfully develop with respect to which we retain development and commercialization rights,~~ we could face a number of additional risks, including: • scaling and retaining our global sales, marketing and administrative infrastructure and capabilities; • hiring, training, managing and supervising our personnel worldwide; • the cost of further developing, or leveraging an established, marketing or sales force, which may not be justifiable in light of the revenues generated by any particular product and / or in any specific geographic region; and • our direct sales and marketing efforts may not be successful. If we are unable to continue to develop and scale our own global marketing, sales, market access and distribution capabilities for our current and any future products, we will not be

able to successfully commercialize our products without reliance on third parties. The patient populations suffering from hATTR amyloidosis with polyneuropathy, **ATTR amyloidosis with cardiomyopathy,** AHP and PH1 ~~are small and~~ have not been established with precision. If the actual number of patients suffering from these diseases is smaller than we estimate, or if we fail to raise awareness of these diseases and diagnosis is not improved, our business, prospects, operating results and financial condition may be adversely affected. Our estimates regarding the potential market size for ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any future products **that** ~~at the time~~ we ~~commence~~ **may** ~~commercialization~~ **commercialize** , may be materially different from the actual market size, including as a result of the indication approved by regulatory authorities, which could result in significant changes in our business plan and may have a material adverse effect on our business, prospects, operating results and financial condition. **If** ~~In addition, our efforts to raise disease awareness and improve diagnosis of our relevant disease states were impacted by the COVID- 19 pandemic. For example, in 2020 and 2021, we saw a reduction in peer- to- peer educational opportunities, reduced physician attendance at congresses and symposia and overall opportunities for physician engagement. As is the case with most orphan diseases, if~~ we are unable to **accurately estimate the number of patients suffering from a disease for which we** successfully **commercialize a product or we were not able to** raise awareness of these diseases and improve diagnosis, it could have a material adverse effect on our business, prospects, operating results or financial condition, and it will be more difficult or impossible to achieve profitability. Any products we currently market or may develop in the future may become subject to unfavorable pricing regulations, third- party reimbursement practices or healthcare reform initiatives, thereby harming our business, prospects, operating results and financial condition. The regulations that govern marketing approvals, coverage, pricing and reimbursement for new drugs vary widely from country to country and are subject to change. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing authorization or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. We are actively monitoring these regulations as we market and sell our approved products and as several of our product candidates move through late stages of development. However, a number of our product candidates are currently in the earlier stages of development, and we will not be able to assess the impact of such regulations or any changes to such development programs for a number of years. We might also obtain regulatory approval for a product, including one or more of our approved products, in a particular country, but then be subject to price regulations or price controls that delay our commercial launch of the product and / or negatively impact the revenues we are able to generate from the sale of the product in that country and potentially in other countries due to reference pricing. We believe that the efforts of governments and third- party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. In the U. S., **healthcare and** pharmaceutical pricing ~~is~~ **are** subject to both government and public scrutiny and calls for reform, and the U. S. government ~~has continued~~ **continues** to ~~focus~~ **propose** on legislative and regulatory changes designed to control costs. Specifically, there have been several recent U. S. Congressional inquiries into prescription drugs, and proposed and enacted federal and state legislation and regulations designed to, among other things, bring more transparency to drug pricing, reduce the cost **and reimbursement** of prescription drugs under ~~Medicare~~ **third- party payor programs** , ~~review the relationship between pricing~~ and **alter the nature and operation of** manufacturer patient **support** programs ~~, and reform government program reimbursement methodologies for drugs~~ . These developments could, directly or indirectly, affect our ability to sell ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or future products, if approved, at a favorable price. At the federal level, for example, the **Inflation Reduction Act, or** IRA **,** includes several provisions that will impact our business to varying degrees. For example, the IRA may require us to pay rebates if we increase the **net** cost of a Medicare Part B or Part D drug faster than the rate of inflation. In addition, our cost- sharing responsibility for any approved product covered by Medicare Part D could be significantly greater under the **IRA** ~~newly designed~~ Part D benefit structure compared to the pre- IRA benefit design. Under the IRA' s Price Negotiation Program, ~~a~~ **an** FDA approval for vutrisiran for treatment of Stargardt Disease would cause us to lose the orphan exemption for AMVUTTRA from Medicare price negotiation. As a result, in October 2022, we announced we would not pursue a Phase 3 clinical trial to study vutrisiran for **the** treatment of Stargardt Disease. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties or a potential excise tax. The effect of the IRA on our business and the healthcare industry in general continues to ~~develop~~ **evolve** and **we** may ~~have~~ **continue to discover** additional adverse impacts on our company or our industry. The IRA is anticipated to have significant effects on the pharmaceutical industry and may reduce the prices we can charge and reimbursement we can receive for our products, among other effects. Furthermore, the ~~Biden~~ **new** administration has indicated that lowering prescription drug prices is a priority, but ~~we do not know~~ the **nature and** impact of ~~policies established by~~ **any potential policy changes remain uncertain. While frameworks like the IRA aim to control costs,** ~~the~~ **their** ~~Biden~~ **implementation under the new** administration ~~to lower the~~ **could introduce further regulatory changes, such as additional** ~~prices~~ **price** ~~of prescription drug prices.~~ **restrictions on products we sell to Medicare** ~~For~~ **or** ~~example, the~~ **other** ~~Center~~ **government purchasers. Any such developments could adversely affect reimbursement, competitive dynamics, and our business. We continue to monitor legislative reforms and assess their potential impact on our operations, but we cannot predict their ultimate effect on our business. Additionally, the new administration may propose policy changes that create additional uncertainty** for **our business. These may include new price restrictions on products we sell to** Medicare ~~and Medicaid Innovation is developing new models intended to lower drug costs under Medicare and Medicaid, including designing new payment methods for~~ **or** ~~drugs approved via FDA' s accelerated approval pathway, creating a list of generic drugs for which the out- of- pocket Part D costs will be capped at $ 2 a month per drug, and establishing new approach for administering outcomes- based agreements for cell and gene therapies. We do not know what additional steps the Biden administration may take to attempt to lower prescription drug prices or the impact of such steps. Although a number of these and~~ other **government**

purchasers ~~proposed measures may require authorization through additional legislation to become effective~~ , ~~and~~ **or** ~~the~~ **other regulatory** ~~current U. S. presidential administration may reverse or otherwise change~~ **changes impacting reimbursement or competitive dynamics in multisource markets** ~~these measures, both the current U. S. presidential administration and Congress have indicated that they will continue to seek new measures to control drug costs~~ . At the state level, governments have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing. Some of these measures include ~~restricting price, reimbursement, discounts,~~ **upper payment limits on state- regulated payers; regulating** product access **, copayment assistance** , and marketing; imposing drug price, cost, and marketing disclosure and transparency requirements; permitting importation from other countries; and encouraging bulk purchasing. For example, on January 5, 2024, the FDA authorized Florida' s Agency for Health Care Administration' s drug importation proposal, the first step toward Florida facilitating importation of certain prescription drugs from Canada. ~~Importation~~ **We cannot predict how further developments** of **or changes to** ~~drugs from Canada and the~~ **these policies** ~~Most Favored Nation, or MFN, Model may materially~~ and ~~adversely~~ **rules will** affect ~~the price we receive for any of~~ our **business** ~~commercially approved products~~ . In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ~~ultimate~~ demand for our products, once approved, or put pressure on our product pricing. We cannot predict what healthcare reform initiatives may be adopted in the future in the U. S. or other foreign countries. Further federal, state and foreign legislative and regulatory developments are likely, **with** ~~and we expect~~ **expected** ~~ongoing initiatives in the U. S. to increase~~ **increased** pressure on drug pricing. Such reforms could have a material and adverse effect on our anticipated revenues ~~from~~ **for** one or more of our approved products or other product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our business, prospects, operating results and financial condition and our ability to develop drug candidates. Our ability to commercialize our approved products or any future products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third- party payors such as government health administration authorities, private health insurers and other organizations. One or more of our approved products and any other products for which we are able to obtain marketing approval may not be considered medically necessary or cost- effective, and the amount reimbursed may be insufficient to allow us to sell such product (s) or any future products on a competitive basis or realize an appropriate return on our investment in product development. There may be significant delays in obtaining coverage for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or foreign regulatory authorities. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution or that covers a particular provider' s cost of acquiring the product. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on lower- cost drugs that are already marketed, covered, and reimbursed, may be incorporated into existing payments for other services, and may reflect budgetary constraints or imperfections in data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U. S. In particular, governments in certain markets such as in EU, the U. K., Japan, and China, provide healthcare at low (or zero) direct costs to consumers at the point of care, and thus have significant power as large single payers to regulate prices or impose other cost control mechanisms. In addition, the emphasis on managed care in the U. S. has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third- party reimbursement rates and pharmaceutical pricing regulations may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Increasingly, the third- party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for drug products. In the U. S., we have entered into ~~over 40~~ value- based agreements, or VBAs, and are negotiating additional VBAs with commercial health insurers. The goal of these agreements is to ensure that we are paid based on the ability of our commercially approved products to deliver results in the real **-** world setting comparable to those demonstrated in our clinical trials, and the agreements are structured to link the performance of our approved products in real- world use to financial terms. Partnering with payors on these agreements is also intended to provide more confidence regarding the value of our products and help accelerate coverage decisions for patients. If the payment we receive for our products, or the reimbursement provided for such products, is inadequate in light of our significant development and other costs, or if reimbursement is denied, our return on investment could be adversely affected. In addition, we have stated publicly that we intend to grow through continued scientific innovation rather than ~~arbitrary~~ **more substantial** price increases. Specifically, we have stated that we will not raise the price of any product for which we receive marketing approval over the rate of inflation, as determined by the consumer price index for urban consumers (approximately 3. ~~4~~ **5** % currently ~~)~~) absent a significant value driver. Our patient access philosophy could also negatively impact the revenues we are able to generate from the sale of one or more of our products in the future. Insurers are increasingly adopting programs and policies that limit access to medications and increase out- of- pocket costs for patients. In the U. S., to help patients access and afford our approved product (s), we may utilize programs to assist them, including patient assistance programs and co- pay coupon programs for eligible patients. It is possible that changes in insurer policies regarding co- pay coupons (such as co- pay accumulator and maximizer programs) and patient assistance programs (such as alternative funding programs) and / or the introduction and enactment of new legislation or regulatory action could restrict or otherwise negatively affect these co- pay coupon programs and patient support programs, which could result in fewer patients using affected products, and therefore could have a material adverse effect on our sales, business, and financial condition. We are subject to U. S. and certain foreign

export and import controls, sanctions, embargoes, anti- corruption laws, and anti- money laundering laws and regulations. Failure to comply with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business. We are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Control, and anti- corruption laws, including the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, the UK Bribery Act 2010, and other applicable anti- bribery and anti- money laundering laws. Anti- corruption laws are interpreted broadly and prohibit companies and their officers, directors, employees, agents, contractors, and other third- party representatives from directly or indirectly authorizing, promising, offering, providing, soliciting, or receiving payments or anything else of value in order to improperly influence the acts or decisions of recipients in the public or private sector or to secure any other improper advantage to obtain or retain business. From time to time, we may engage third parties to conduct clinical trials outside of the U. S., to sell our products abroad, and / or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government- affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of agents, contractors, and third- party representatives acting on our behalf, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial fines and penalties, reputational harm, and other adverse consequences. We remain focused on these laws and the activities they regulate and ~~, as detailed below,~~ maintain a global compliance program designed to empower our business to operate in compliance with their requirements. Governments outside the U. S. may impose strict price controls, which may adversely affect our revenues. The pricing of prescription pharmaceuticals is also subject to governmental control outside the U. S. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies, which is time- consuming and costly. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired. In some countries, including Member States of the EU, or Japan, the pricing of prescription drugs may be subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, governments and other stakeholders can put considerable pressure on prices and reimbursement levels, including as part of cost containment measures. Moreover, political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low- priced and high- priced countries, can further reduce prices. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. Publication of discounts by third- party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our collaborators and the potential profitability of our approved products or any future products in those countries would be negatively affected. We could also suffer impact from tightening pricing controls on account of greater competition from less expensive generic or biosimilar products once patent or other exclusivity expires. Certain governments have adopted policies to switch prescribed products to generic versions to reduce costs. If we or our collaborators, CMOs or service providers fail to comply with healthcare laws and regulations, ~~or legal obligations~~ **including but not limited to those** related to **fraud** ~~privacy, data protection~~ and **abuse** ~~information security~~, we or they could be subject to enforcement actions, which could negatively impact our ability to develop, market and sell our products and may harm our reputation. Healthcare providers, physicians, and third- party payors play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our existing and future arrangements with third- party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain our business or financial arrangements and relationships through which we market, sell, and distribute our products. ~~Restrictions under applicable~~ **In the United States, these laws include, without limitation,** federal and state ~~healthcare~~ **fraud and abuse** laws **, transparency laws and patient data privacy and security laws** and regulations **,** ~~include~~ **including but not limited to** the following: • The U. S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration ~~(including any kickback, bribe or rebate)~~, directly or indirectly, overtly or covertly, in cash or in kind, to induce ~~, or in return~~ **either the referral of an individual** for, **or** the purchase **or** ~~, lease, order~~ **ordering** ~~, arrangement, or recommendation~~ of ~~any~~ **, a** good ~~, facility, item~~ or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs ~~. A person or entity does not need to have actual knowledge of the federal Anti- Kickback Statute or specific intent to violate it to have committed a violation~~. Violations are subject to civil and criminal fines and penalties, imprisonment, and exclusion from government healthcare programs. ~~In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal FCA or federal civil money penalties.~~ • The U. S. federal false claims laws, including the FCA, which **generally** prohibit ~~, among other things~~, individuals or entities from knowingly presenting or causing to be presented, claims for payment **for good or services** by government- funded programs such as Medicare or Medicaid that are false or fraudulent ~~, making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government~~. Manufacturers can be held liable under the FCA even when they

do not submit claims directly to government payors if they are deemed to " cause " the submission of false or fraudulent claims. ~~The FCA also permits a private individual acting as a " whistleblower " to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery.~~ Penalties are three times the amount of the claims in question plus civil monetary penalties. • The federal civil monetary penalties laws, which **generally** impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or Medicaid beneficiary if the person knows or should know it is likely to influence the beneficiary' s selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or Medicaid **. Conduct regulated by the federal civil monetary penalties law often overlaps with other healthcare laws** , ~~unless an exception applies~~ **including the federal Anti- Kickback Statute** . • The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which ~~created, among~~ **in addition to privacy and security protections applicable to healthcare providers and** other ~~provisions~~ **entities** , ~~federal criminal statutes that prohibit~~ **prohibits** ~~knowingly and willfully~~ executing, or attempting to execute, a scheme to defraud any healthcare benefit program ~~or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e. g., public or private)~~ and ~~, in any matter involving a health care benefit program, knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or~~ making ~~any materially~~ false statements **relating to** ~~in connection with the delivery of, or payment for,~~ healthcare **matters** ~~benefits, items or services. Similar to the federal Anti- Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it. • HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, including its implementing regulations, which impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and requires notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information~~ . • Federal " sunshine " requirements imposed ~~by the Affordable Care Act~~ on drug, device, ~~biological~~ and medical supply manufacturers when payment is available under Medicare, Medicaid or the Children' s Health Insurance Program ~~(with certain exceptions)~~ to report annually to **HHS** ~~Health and Human Services under the Open Payments Program,~~ information regarding any ~~payment or other~~ " transfer of value " made or distributed to **healthcare** ~~physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non- physician~~ providers ~~such as physician assistants~~ and **organizations** ~~nurse practitioners, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members~~ . Failure to submit timely, accurate and complete information may result in civil monetary penalties. • Federal price reporting laws, which **, among other requirements,** require manufacturers to calculate ~~and ,~~ report **, and certify in a timely manner** complex pricing ~~metrics~~ **and other product data** to government programs, where such reported ~~prices~~ **data** may be used in the calculation of reimbursement and / or discounts on approved **products; and to pay rebates or offer discounts on pharmaceutical** products. • Federal statutory and regulatory requirements applicable to pricing and sales of products to federal government agencies. • Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers **. • The Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug product and medical device marketing, prohibits manufacturers from marketing such products prior to approval or for unapproved indications and regulates the distribution of samples** . • State and foreign laws comparable to each of the above federal laws, including in the EU laws prohibiting giving healthcare professionals any gift or benefit in kind as an inducement to prescribe our products **and** ~~, national~~ transparency laws requiring the public disclosure of payments made to healthcare professionals and institutions, and data privacy laws, in addition to anti- kickback and false claims laws applicable to commercial insurers and other non- federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to **price transparency and** government reimbursement programs ~~,~~ patient data privacy and security. • European privacy laws including Regulation 2016 / 679, known as the General Data Protection Regulation, or the EU GDPR, and the EU GDPR as transposed into the laws of the UK, the UK GDPR, collectively referred to as the GDPR, and the e- Privacy Directive (2002 / 58 / EC), and the national laws implementing each of them, as well as the Public and Electronic Communications Regulations 2003 in the UK and the privacy laws of Japan, Brazil and other territories. • The California Consumer Privacy Act of 2018, as amended by the California Privacy Rights Act of 2020, or, collectively, the CCPA, that, among other provisions, gives California residents rights **to** ~~of access, correction, portability, and deletion of~~ their personal information and ~~various opt out rights. The CCPA also~~ imposes various **privacy and security** obligations on regulated businesses ~~, such as to maintain privacy notices, implement reasonable security practices, and include specific terms in contracts with data processors~~ . ~~The CCPA also created a new state agency that is vested with authority to implement (including through rule making) and enforce the CCPA. The CCPA provides for civil penalties for violations, as well as a limited private right of action for data breaches. •~~ Furthermore, comprehensive privacy laws similar to the CCPA **and consumer health data laws** have been enacted in more than ~~ten~~ **twelve** other states and proposed in ~~several others. Three~~ **nearly one third of all** states ~~have additionally enacted laws regulating " consumer health data, " which impose additional obligations on regulated entities beyond state comprehensive privacy laws, such as to obtain distinct consents for certain collection and sharing of consumer health data, obtain authorization to sell consumer health data, and maintain a consumer health data privacy policy~~ . Washington' s law regulating consumer health data contains a private right of action. The effects of the CCPA and other state privacy laws **, and the creation of new regulatory bodies, such as the California Privacy Protection Agency, increases the cost and complexity of operating our business and our exposure to regulatory investigations, enforcement, fines, and penalties, any of which could negatively impact our business and operations. Failure to comply with these obligations could result in damage to our reputation and legal liability, censures, penalties and fines, disgorgement of profits, restitution to customers, remediation, the issuance of cease- and- desist orders, or injunctive or other equitable relief against us, which individually or in the aggregate could negatively impact our financial results. Depending on the nature of the violation, we may be required to offer restitution or remediation to**

customers, and the cost of doing so could exceed our loss reserves. Analogous state and foreign laws and regulations, such as state anti- kickback, anti- bribery and false claims laws, which may apply to healthcare items or services that are **reimbursed by non- governmental third- party payors, including private insurers, as well as other** ~~potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement and / or litigation. Some~~ state laws ~~also~~ **that** require **companies** ~~pharmaceutical manufacturers~~ to comply with **specific** ~~the pharmaceutical industry' s voluntary~~ compliance **standards** ~~guidelines and the relevant compliance guidance promulgated by the federal government~~ , ~~in addition to~~ **restrict financial interactions between companies and healthcare providers,** ~~requiring~~ **require** ~~manufacturers~~ **companies** to report information related to payments to ~~physicians and other~~ healthcare providers ~~or~~ **,** marketing expenditures ~~and~~ **or** pricing ~~information. State and foreign laws also govern the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating our~~ **or** ~~compliance efforts~~ **require the licensing or registration of sales representatives** . If our operations are found to be in violation of any of the aforementioned requirements, we may be subject to penalties, including civil or criminal penalties (including individual imprisonment), criminal prosecution, monetary damages, the curtailment or restructuring of our operations, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, or the imposition of a corporate integrity agreement with the Office of Inspector General of the Department of **HHS** ~~Health and Human Services~~ , or the OIG, any of which could materially and adversely affect our business, prospects, operating results or financial condition. We remain focused on enhancing our global compliance infrastructure ~~following the commercial launch of our four products over the last four years in the U. S., EU and multiple other geographies, and~~ as we prepare for the launch of our products in additional countries, assuming regulatory approvals. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. For additional information, see the Risk Factor captioned " We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities with respect to our unapproved product candidates or promoting our commercially approved products in a way that violates applicable regulations. " Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management' s attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources. If we or our collaborators, CMOs or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our approved products, or any future products, successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others, civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment. Moreover, federal, state and foreign laws or regulations are subject to change, and while we, our collaborators, CMOs and / or service providers currently may be compliant, we could fall out of compliance due to changes in interpretation, prevailing industry standards or the legal structure **. Activities we undertake related to commercializing our drug products could create risk under laws such as the federal Anti- Kickback Statute and / or the federal False Claims Act, or FCA, with the potential for significant liability, including civil and administrative penalties, criminal sanctions, and potential exclusion from participation in government programs** . Third party patient assistance programs that receive financial support from companies have become the subject of enhanced government and regulatory scrutiny ~~. The OIG has established guidelines that suggest that it is lawful for pharmaceutical manufacturers to make donations to charitable organizations who provide co- pay assistance to Medicare patients~~ , **with** ~~provided that such organizations, among other things, are bona fide charities, are entirely independent of and not controlled by the manufacturer, provide aid to applicants on a first- come basis according to consistent financial criteria and do not link aid to use of a donor' s product. However, donations to patient assistance programs have received negative publicity and have been the subject of multiple government enforcement actions,~~ related ~~to allegations regarding their use to promote branded pharmaceutical products over other less costly alternatives. Specifically, in recent years, there have been multiple settlements resulting from government claims challenging the legality~~ --- **legal risk** ~~of patient assistance programs under a variety of federal and state laws. We have made and may continue to make grants to independent charitable foundations that help financially needy patients with their premium, co- pay, and co- insurance obligations. If we do so, and if we or our donation recipients are deemed to be acting in violation of relevant laws, regulations or evolving government guidance, we could be subject to damages, fines, penalties, or other criminal, civil, or administrative sanctions or enforcement actions~~ . We are subject to governmental regulation and other legal obligations related to privacy, data protection and information security, and we are subject to consumer protection laws that regulate our marketing practices and prohibit unfair or deceptive acts or practices. Our actual or perceived failure to comply with such obligations could harm our business. The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for " special category data, " which includes health, biometric and genetic information of data subjects located in the EEA and UK. Further, GDPR provides a broad right for EEA Member States to create supplemental national laws, such as laws relating to the processing of health, genetic and biometric data, which could further limit our ability to use and share such data or could cause our costs to increase, and harm our business and financial condition. Failure to comply with the requirements of the GDPR and the related national data protection laws of the EEA Member States and the UK, which may deviate slightly from the GDPR, may result in fines of up to 4 % of total global annual revenue, or € 20. 0 million (£ 17. 5 million under the UK GDPR), whichever is greater, and in addition to such fines, we may be the subject of litigation and / or adverse publicity, which could have a material adverse effect on our reputation and business. As a result of the implementation of the GDPR, we are required to implement a number of measures to ensure compliance with the data protection regime. The GDPR (i) requires us to inform data subjects of how we process their personal data and how they can exercise their rights, (ii) requires us to ensure we have a valid

legal basis to process personal data (if this is consent, the requirements for obtaining consent carries a higher threshold), (iii) requires us to appoint a data protection officer where sensitive personal data (i. e., health data) is processed on a large scale, (iv) introduces mandatory data breach notification requirements throughout the EEA and UK, (v) requires us to maintain records of our processing activities and document data protection impact assessments where there is high risk processing, (vi) imposes additional obligations on us when we are contracting with service providers, requires (vii) appropriate technical and organizational measures to be put in place to safeguard personal data and (viii) requires us to adopt appropriate privacy governance including policies, procedures, training and data audit. Significantly, the GDPR imposes strict rules on the transfer of personal data out of the EEA and UK to the U. S. or other regions that have not been deemed to offer " adequate " privacy protections. In the past, companies in the U. S. were able to rely upon the EU- U. S., UK- U. S. and the Swiss- U. S. Privacy Shield frameworks as a basis for lawful transfer of personal data from the EU and the UK to the U. S. In July 2020, the Court of Justice of the European Union, or CJEU, in Case C- 311 / 18 (Data Protection Commissioner v Facebook Ireland and Maximillian Schrems, or Schrems II) invalidated the EU- U. S. Privacy Shield on the grounds that the Privacy Shield failed to offer adequate protections to EU personal data transferred to the U. S. The CJEU, in the same decision, deemed that the Standard Contractual Clauses, or SCCs, published by the EC are valid. However, the CJEU ruled that transfers made pursuant to the SCCs need to be assessed on a case- by- case basis to ensure the law in the recipient country provides " essentially equivalent " protections to safeguard the transferred personal data as the EU, and required businesses to adopt supplementary measures if such standard is not met. Subsequent guidance published by the European Data Protection Board, or EDPB, in June 2021 described what such supplementary measures must be, and stated that businesses should avoid or cease transfers of personal data if, in the absence of supplementary measures, equivalent protections cannot be afforded. On June 4, 2021, the EC published new versions of the SCCs, which seek to address the issues identified by the CJEU' s Schrems II decision and provide further details regarding the transfer assessments that the parties are required to conduct when implementing the new SCCs. However, there continue to be concerns about whether the SCCs and other mechanisms will face additional challenges. Similarly, in September 2020, the Swiss data protection authority determined the Swiss- U. S. Privacy Shield framework was no longer a valid mechanism for Swiss- U. S. data transfers and raised questions about the validity of the SCCs as a mechanism for transferring personal data from Switzerland. While SCCs provide an alternative to our Privacy Shield certification for EU- U. S. data flows, the decision (and certain regulatory guidance issued in its wake) casts doubt on the legality of EU- U. S. data flows in general. Any inability to transfer, or burdensome restrictions on the ability to transfer, personal data from the EU to the U. S. in compliance with applicable data protection laws may impede our ability to conduct clinical trials and may adversely affect our business, prospects, operating results and financial condition. The UK is not subject to the EC' s new SCCs but has published its own transfer mechanism, the International Data Transfer Agreement or International Data Transfer Addendum, which enables transfers from the UK. On March 25, 2022, the EC and the U. S. announced a political agreement on a new " Trans- Atlantic Data Privacy Framework " to replace the invalidated Privacy Shield. The framework introduced new binding safeguards to address the concerns raised by the CJEU in Schrems II. On July 10, 2023, the EC announced that it had adopted its adequacy decision for that data privacy framework, labelled the EU- U. S. Data Privacy Framework. The adequacy decision concluded that the U. S. ensures an adequate level of protection for personal data transferred from the EU to US companies under the new framework, and the EC stated that as a result personal data can flow safely from the EU to US companies participating in the framework, without having to put in place additional data protection safeguards. The EU- U. S. Data Privacy Framework is subject to periodic reviews, to be conducted by the EC, together with other European data protection authorities and U. S. authorities, with the first review to take place within a year of adoption of the adequacy decision. A case has been lodged with and remains pending before the EU courts challenging the validity of the EU- U. S. Data Privacy Framework. EEA Member States have adopted implementing national laws to implement the GDPR which may partially deviate from the GDPR and the competent authorities in the EEA Member States may interpret GDPR obligations slightly differently from country to country, and we do not expect to operate in a uniform legal landscape in the EU. In addition, the UK Government has now introduced a Data Protection and Digital Information Bill, or the UK Bill, into the UK legislative process. The aim of the UK Bill is to reform UK' s data protection regime following Brexit. If passed, the final version of the UK Bill may have the effect of further altering the similarities between the UK and EEA data protection regime. The anticipated UK general election in 2024 could postpone passage of the UK Bill. We are subject to the supervision of local data protection authorities in those jurisdictions in which we are monitoring the behavior of individuals in the EEA or UK (i. e., undertaking clinical trials). We depend on a number of third parties in relation to the provision of our services, a number of which process personal data of EU and / or UK individuals on our behalf. With each such provider we enter or intend to enter into contractual arrangements under which the provider is contractually obligated to only process personal data according to our instructions, and conduct or intend to conduct diligence to ensure that they have sufficient technical and organizational security measures in place. We are also subject to evolving European privacy laws on electronic marketing and cookies. The EU is in the process of replacing the e- Privacy Directive (2002 / 58 / EC) with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each European member state, without the need for further enactment. While the e- Privacy Regulation was originally intended to be adopted on May 25, 2018 (alongside the GDPR), it is still going through the European legislative process. Draft regulations were rejected by the Permanent Representatives Committee of the Council of EU on November 22, 2019; it is not clear when, or even if, new regulations will be adopted. We are also subject to current and evolving privacy laws in other foreign countries, such as Canada. Compliance with U. S. and international data protection laws and regulations requires that we take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, and, in some cases, impacts our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and / or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects, employees and

other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time- consuming to defend and could result in adverse publicity that could harm our business. Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending and services, and any inability on our part to effectively adapt to such changes could substantially affect our business, prospects, operating results and financial condition. Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $ 1. 2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year, starting in 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. ~~Due to~~ **Under federal** legislation ~~amending the statute~~, including the Bipartisan Budget Act of 2018, these reductions **, while temporarily altered due to the COVID- 19 pandemic, have resumed as of July 1, 2022 and** will stay in effect through ~~2030~~ **2032** unless additional Congressional action is taken. ~~Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, as well as subsequent legislation, these reductions were suspended from May 1, 2020 through December 31, 2021 due to the COVID- 19 pandemic. Following the suspension, a 1 % payment reduction began on April 1, 2022, lasting through June 30, 2022. The 2 % payment reduction resumed on July 1, 2022.~~ The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. **Further, the American Rescue Plan Act of 2021 increased the budget deficit such that additional sequestration was required under the Statutory Pay- As- You- Go Act of 2010, which led to a further payment reduction, up to 4 %, that was to take effect in January 2022, although implementation of the reduction was delayed until 2025.** These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for our approved products or any of our product candidates for which we may obtain regulatory approval, or the frequency with which our products or any future product is prescribed or used. **It is uncertain how current and future reforms, including any new legislation enacted during the new administration, in these areas will influence the future of our business operations and financial condition.** Previous actions taken by Congress to reduce spending, disagreements in Congress over government funding levels, high ~~-~~levels of government debt, and the Medicare Trustees' warnings about the programs' sustainability as presently structured suggest that uninterrupted / continued growth in funding for relevant programs is not guaranteed. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell our approved products and any other products we may develop. If we fail to comply with our obligations under the 340B Drug Pricing Program ~~or~~ **and** other U. S. governmental pricing programs, we could be subject to **legal consequences** ~~additional reimbursement requirements~~ **, including** penalties, sanctions and fines, which could have a material adverse effect on our business, prospects, operating results and financial condition. We participate in the 340B Drug Pricing Program, Medicaid Drug Rebate Program, and a number of other federal and state government ~~pricing~~ programs in the U. S. **Participation in some of these programs is required** in order to obtain ~~coverage for~~ **reimbursement of** our **drug** products ~~by certain government health care programs~~ **under Medicaid or Medicare Part B** . These programs generally require that we provide discounts or pay rebates to certain payers when our products are dispensed to beneficiaries of these programs. **To support the calculation of** ~~These~~ **these discounts and rebates, these** programs may also impose **periodic and special** ~~other requirements, including certain~~ price **and product data** reporting requirements. Changes to our obligations under these government pricing programs occur frequently and program requirements are often ambiguous. **Pricing calculations are complex, vary across programs and may be subject to evolving interpretations by legislative and regulatory bodies and the courts.** We may be or become subject to penalties **for noncompliance, including, but not limited to, civil monetary penalties, exposure under the federal false claims act, and termination from the government program,** as a result of our failure to comply with obligations under these programs, including if we fail to provide timely **, complete** and accurate information to the government, to pay the correct rebates, or to offer the correct discounted pricing. **In addition, potential policy changes by the new administration may introduce additional uncertainty for our business. These could include changes to the level of scrutiny applied by the Health Resources and Services Administration to enforce non- compliance with the 340B Drug Pricing Program, new price restrictions on products we sell to Medicaid, Medicare or other government purchasers, or other regulatory changes impacting reimbursement or competitive dynamics in multisource markets. Any such policy shifts could significantly impact our business and operations. Increasingly, states are enacting legislation requiring manufacturers to report drug pricing information. However, states have not always clearly defined their reporting requirements, resulting in manufacturers failing to properly disclose the required pricing information.** Complying with ~~these~~ **federal and state** programs and future changes to these programs can be **complex and** cost- and resource- intensive **,** and could have a material adverse effect on our business, prospects, operating results and financial condition. There is a substantial risk of product liability claims in our business. If we are unable to obtain sufficient insurance, a product liability claim against us could adversely affect our business, prospects, operating results and financial condition. Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. Such claims might not be fully covered by product liability insurance. In addition, product liability claims could result in an FDA investigation of the safety and effectiveness of our approved products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the

merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management' s time and our resources, substantial monetary awards to trial participants or patients and a decline in our stock price. We currently have product liability insurance that we believe is appropriate for our stage of development, including the marketing and sale of our approved products. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business. Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements or insider trading violations, which could significantly harm our business, prospects, operating results and financial condition. We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with governmental regulations, including healthcare fraud and abuse and anti- kickback laws and regulations in the U. S. and abroad, or failure to report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self- dealing and other abusive practices. As discussed in the Risk Factor **above** captioned " If we or our collaborators, CMOs or service providers fail to comply with healthcare laws and regulations, or legal obligations related to privacy, data protection and information security, we or they could be subject to enforcement actions, which could negatively impact our ability to develop, market and sell our products and may harm our reputation, " these laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including improper trading based upon, **material** information obtained in the course of clinical ~~studies~~ **trials or other material non- public information** , which could result in regulatory sanctions and serious harm to our reputation. We maintain a global compliance program and remain focused on its evolution and enhancement. Our program includes efforts such as risk assessment and monitoring, fostering a speak- up culture encouraging employees and third parties to raise good faith questions or concerns, and defined processes and systems for reviewing and remediating allegations and identified potential concerns. It is not always possible, however, to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, prospects, operating results and financial condition, including the imposition of significant fines or other sanctions. If we do not comply with laws regulating the protection of the environment and health and human safety, our business, prospects, operating results and financial condition could be adversely affected. Our research, development and manufacturing **activities** involve the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge and Norton that are required for our research, development and manufacturing activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing these materials in our Cambridge and Norton facilities comply with the relevant guidelines of the City of Cambridge, the town of Norton, the Commonwealth of Massachusetts and the Occupational Safety and Health Administration of the U. S. Department of Labor. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood- borne pathogens and the handling of biohazardous materials. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate, any of these laws or regulations. Our success depends, in part, on our ability to protect proprietary compositions, methods and technologies that we develop under the patent and other intellectual property laws of the U. S. and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to manufacture and commercialize our ~~proposed~~ **current and future** products. Because certain U. S. patent applications are confidential until the patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date ~~which~~ **that** will not be filed in foreign countries, third parties may have filed patent applications for subject matter covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we or our collaborators may be required to obtain licenses under third- party patents to market one or more of our or our collaborator' s approved products, or further develop and commercialize future products, or continue to develop product candidates in our pipeline being developed by us or our collaborators. If licenses are not available to us or not available on reasonable terms **or at all** , we or our licensees may not be able to market the affected products or conduct the desired activities. Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we may rely on third- party collaborators to file patent applications relating to proprietary technology that we develop jointly as part of collaborations. The process of obtaining patent protection is expensive and time- consuming. If we or our ~~present or future~~ collaborators fail to file

and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business may be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management, could reduce or eliminate milestone and / or royalty payments to us from third party licensors and could have a material adverse effect on our business. Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the U. S. and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the U. S. Congress and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act, or AIA, included a number of changes to the patent laws of the U. S. If any of the enacted changes do not provide adequate protection for discoveries, including our ability to pursue infringers of our patents for substantial damages, our business could be adversely affected. One major provision of the AIA, which took effect in March 2013, changed U. S. patent practice from a first- to- invent to a first- to- file system. If we fail to file an invention before a competitor files on the same invention, we no longer have the ability to provide proof that we were in possession of the invention prior to the competitor' s filing date, and thus would not be able to obtain patent protection for our invention. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents. Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. We also rely to a certain extent on trade secrets, know- how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know- how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business, prospects, operating results and financial condition could be materially adversely affected. Failure to obtain and maintain broad patent scope and all available regulatory exclusivities and to maximize patent term restoration or extension on patents covering our **products and** product candidates ~~and products~~ may lead to loss of exclusivity and generic entry resulting in a loss of market share and / or revenue ~~. We license patent rights from third- party owners. If such owners do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, our competitive position and business, prospects, operating results and financial condition may be harmed~~ . 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. In particular, we have obtained licenses from, among others, Ionis, Arbutus, and Dicerna. We **may** also ~~intend to~~ enter into additional licenses to third- party intellectual property in the future. Our success will 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 we have licensed. Even if patents issue 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, operating results and financial condition. In addition, we sublicense our rights under various third- party licenses to our collaborators. Any impairment of these sublicensed rights could result in reduced revenues under our collaboration agreements or result in termination of an agreement by one or more of our collaborators. RNAi is a relatively new **and growing** scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi patents and have licensed many of these patents from third parties on an exclusive basis. The issued patents and pending patent applications in the U. S. and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics. Specifically, we have a portfolio of patents, patent applications and other intellectual property covering, among other things: fundamental aspects of the structure and uses of siRNAs, including their use as therapeutics, and RNAi- related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic and other uses; siRNAs directed to specific targets as treatments for particular diseases; delivery technologies, such as in the fields of carbohydrate conjugates and cationic liposomes; and all aspects of our specific development candidates. As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, re- examination and opposition proceedings, as well as pre- and post- grant review proceedings in various patent offices relating to patent rights in the RNAi field. In addition, third parties may challenge the validity of our patents. ~~For example, a third party has filed an opposition in the European Patent Office, or EPO, against our owned patent EP 2723758, with claims directed to RNAi compositions and methods for silencing ANGPTL3, arguing that the granted claims are invalid. Following an oral hearing in February 2021, the patent was revoked. A notice of appeal of the EPO' s decision was filed in June 2021 and following an oral hearing in November 2023, the appeal was dismissed resulting in the patent remaining revoked. In March 2022, a third party filed an opposition with the EPO against our owned patent EP3105332, which is directed to RNAi~~

~~compositions and methods for silencing ketohexokinase, seeking to revoke the patent. In addition, in February 2023, a third party filed an opposition with the EPO against our owned patent EP 3366775, titled " Modified RNA Agents " seeking to revoke the patent. Oral hearings are anticipated in these proceedings at times to be determined by the EPO. Additionally, the validity of two Chinese patents (ZL201380063930. 5 and ZL201810143112. 0) relating to inclisiran were challenged by a third party in China. The China National Intellectual Property Administration recently issued decisions confirming that patent No. ZL201380063930. 5 remained valid as a whole, and patent No. ZL201810143112. 0 remained valid based on the amended version of the claims we submitted.~~ We expect that ~~additional oppositions will be filed in the EPO and elsewhere, and other~~ challenges will be raised relating to ~~other~~ patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business, prospects, operating results and financial condition if we are not successful in defending the patentability and scope of our pending and issued patent claims. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business, prospects, operating results and financial condition and on our ability to successfully compete in the field of RNAi. There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need for our siRNA products marketed by us or our licensees, our late- stage therapeutic candidates being developed by us or our collaborators, including zilebesiran and fitusiran, as well as our other pipeline products. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. In addition, there may be issued and pending patent applications that may be asserted against us in a court proceeding or otherwise based upon the asserting party' s belief that we may need such patents for our siRNA therapeutic candidates or marketed products, or to further develop and commercialize future products, or to continue to develop candidates in our pipeline that are being developed by us or our collaborators. Thus, it is possible that one or more organizations will hold patent rights to which we may need a license, or hold patent rights which could be asserted against us. If those organizations refuse to grant us a license to such patent rights on reasonable terms or at all and / or a court rules that we need such patent rights that have been asserted against us, we may be unable to market our products, including ONPATTRO, AMVUTTRA, GIVLAARI or OXLUMO, or to perform research and development or other activities covered by such patents. For example, **on December 12** ~~during 2017 and 2018~~, **2024** ~~Silence Therapeutics~~, ~~plc~~ **the Board of Regents of the University of Texas System**, or ~~Silence~~ **the University of Texas**, filed ~~claims~~ **a lawsuit** in ~~several jurisdictions, including~~ the ~~High~~ **United States District** Court **for the Western District** of **Texas** ~~England and Wales~~, **alleging** ~~and named us and our wholly owned subsidiary Alnylam UK Ltd. as co- defendants. Silence alleged various claims, including~~ that **we infringe one of the University of Texas' patents by making, using and commercializing** ONPATTRO ~~infringed one or more Silence patents. There were also a number of related actions brought by us or Silence~~ in ~~connection with this intellectual property dispute. In December 2018, we entered into a Settlement and License Agreement with Silence, resolving all ongoing claims, administrative proceedings, and regulatory proceedings worldwide between us regarding, among other~~ -- **the U. S** ~~issues, patent infringement, patent invalidity and breach of contract~~. If we become involved in intellectual property litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, and in the case of such litigation or proceedings against us, substantial liability for damages or be required to stop our product development and commercialization efforts. Third parties may sue us for infringing their patent rights. For example, **on December 12, 2024,** ~~in October 2017 Silence sued us in~~ the ~~UK~~ **Board of Regents of the University of Texas System, or the University of Texas, filed a lawsuit in the United States District Court for the Western District of Texas,** alleging that **we infringe one of the University of Texas' patents by making, using and commercializing** ONPATTRO ~~and in other~~ -- **the U** ~~investigational RNAi therapeutics we or MDCO were developing infringed one or more Silence patents~~. **S** ~~In December 2018 we and Silence settled all ongoing litigation between us~~. A third party may also claim that we have improperly obtained or used its confidential or proprietary information. Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, The University of Utah, or Utah, filed a complaint against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e. V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and the University of Massachusetts, claiming that a professor of Utah was the sole inventor, or in the alternative, a joint inventor of certain of our in- licensed patents. Utah was seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. After several years of court proceedings and discovery, the court granted our motions for summary judgment and dismissed Utah' s state law damages claims. During the pendency of this litigation, ~~as well as the Dicerna litigation described below,~~ we incurred significant costs, and in each case, the litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities. **On July 12, 2024, Acuitas Therapeutics Inc., or Acuitas, filed a declaratory judgment action against us in the U. S. District Court for the District of Delaware, seeking a judgment adding certain Acuitas employees as co- inventors on the patents we have asserted against Pfizer / BioNTech and Moderna in our lawsuits described below. On September 19, 2024, we filed a motion to dismiss arguing that Acuitas did not have standing to sue and failed to state a claim upon which relief could be granted. The court has not yet ruled on our motion.** We may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others or protect our proprietary information and trade secrets ~~. For example, during the second quarter of 2015, we filed a trade secret misappropriation lawsuit against Dicerna to protect our rights in the RNAi assets we purchased from Merck Sharp & Dohme Corp., or Merck. In April 2018, we and Dicerna settled all claims in the litigation between us~~. In March 2022, we announced that we separately filed suit in United States District Court for the District of Delaware against Pfizer and Moderna seeking damages for infringement of U. S. Patent No. 11, 246, 933, or the' 933 patent in the parties' manufacture and sale of their messenger RNA, or mRNA, COVID- 19 vaccines. Pfizer joined BioNTech

SE, or BioNTech, to the suit and filed counterclaims. In July 2022, we filed an additional lawsuit in United States District Court for the District of Delaware against each of Pfizer / BioNTech and Moderna seeking damages for infringing U. S. Patent No. 11, 382, 979, or the' 979 patent. The court combined the two patents in a single suit for each of Pfizer / BioNTech, or the 2022 Lawsuit, and Moderna with trial dates set for each in November 2024. On May 26, 2023, we filed additional lawsuits against Pfizer and Moderna in Delaware seeking damages for infringing U. S. Patent No. 11, 590, 229 in the United States District Court for the District of Delaware. In addition to this patent, we added U. S. Patent Nos. 11, 633, 479 **, or the ' 479 patent,** and 11, 633, 480 in the more recently filed suits against both Pfizer and Moderna and ~~also~~ **of** U. S. Patent No. 11, 612, 657 against Pfizer only. On August 9, 2023, a Markman hearing was held in the U. S. District Court for the District of Delaware to consider the meaning of three disputed terms as used in the' 933 and' 979 patents, and on August 21, 2023, the court issued an order construing two of the three terms, and deferred a ruling on the third term **pending an evidentiary hearing, which was held on January 4, 2024 with the final ruling deferred pending the outcome of an additional hearing, which was held on July 12, 2024** . ~~Subsequently~~ **Following the August 21, 2023 order** , we and Moderna jointly agreed to final judgment of non- infringement of two of our patents, and that judgment was entered by the court on August 30, 2023, and on September 7, 2023, we appealed the claim construction ruling to the Court of Appeals for the Federal Circuit in the 2022 lawsuit against Moderna. The claim construction ruling **initially** did not affect one of the patents in the lawsuit filed against Moderna on May 26, 2023, ~~and that~~ **but following a Markman hearing held on August 15, 2024, the court entered a ruling on September 10, 2024, in the same manner as in the other earlier** case **and** ~~is going forward~~ on ~~a schedule with~~ **October 2, 2024, we** ~~an~~ **and** ~~anticipated trial date in~~ **Moderna jointly agreed to final judgment of non- infringement of the ' 479 patent. On October 16, 2024, Moderna filed a motion seeking recovery of fees incurred by** ~~the~~ **them** ~~latter half~~ **from the time we agreed to a judgment** of **non- infringement in the first case until the time we agreed to a judgment of non- infringement in the second case, which period runs from approximately September** ~~2025~~ **2023 to October 2024** . ~~In~~ **We opposed the motion in a reply on November 6, 2024. The court has yet to rule on the motion. The two separate suits against Pfizer / BioNTech are ongoing and in** September 2023, we and Pfizer / BioNTech agreed to consolidate the 2022 ~~Lawsuit~~ and 2023 lawsuits into one case, **with a** ~~which will require moving the~~ trial date **set for July 7,** ~~from November 2024 to the first half of~~ 2025 ~~, with the final schedule to be determined by the court. On January 4, 2024 a hearing was held in the consolidated Pfizer / BioNTech case to construe a final claim term with the final ruling pending~~ . The aforementioned patents relate to our biodegradable cationic lipids that are foundational to the success of the mRNA COVID- 19 vaccines. In protecting our intellectual patent rights through litigation or other means, a third party may claim that we have improperly asserted our rights against them. For example, in August 2017, Dicerna successfully added counterclaims against us in the above- referenced trade secret lawsuit alleging that our lawsuit represented abuse of process and claiming tortious interference with its business. In addition, in August 2017, Dicerna filed a lawsuit against us in the United States District Court of Massachusetts alleging attempted monopolization by us under the Sherman Antitrust Act. As noted above, in April 2018, we and Dicerna settled all claims in the litigation between us. In addition, in connection with certain license and collaboration agreements, we have agreed to indemnify certain third parties for certain costs incurred in connection with litigation relating to intellectual property rights or the subject matter of the agreements. The cost to us of any litigation or other proceeding relating to such intellectual property rights, even if resolved in our favor, could be substantial, and litigation would divert our management' s efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation or legal proceeding could delay our research, development and commercialization efforts and limit our ability to continue our operations. If any parties successfully claim that our creation or use of proprietary technologies infringes upon or otherwise violates their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties' patent rights. In addition to any damages we might have to pay, a court could issue an injunction requiring us to stop the infringing activity or obtain a license from the claimant. Any license required under any patent may not be made available on commercially reasonable terms, or at all. In addition, such licenses are in many instances non- exclusive and, therefore, our competitors may have access to the same technology that is licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or ~~achieve~~ **maintain** profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our ~~collaborations~~ **collaboration agreements** will provide that royalties payable to us for licenses to our intellectual property may be offset by amounts paid by our collaborators to third parties who have competing or superior intellectual property positions in the relevant fields, which could result in significant reductions in our revenues from products developed through collaborations. If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing, commercializing and protecting our RNAi technology, as well as our ~~approved~~ products and product candidates. Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license or render the license non- exclusive, which could result in us being unable to develop, manufacture, market and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, we could incur significant costs and / or disruption to our business and distraction of our management defending against any breach of such licenses alleged by the licensor. For example, in June 2018, Ionis sent us a notice claiming that it was owed ~~payments under~~ **technology access fees,** ~~our~~ **or** ~~second amended~~ **TAFs, based on rights granted** and **amounts paid to us in connection with** ~~restated strategic collaboration and license agreement as a result of~~ the January 2018 ~~restructuring~~ **amendment** of our collaboration agreement with Sanofi and the related Exclusive TTR

License and AT3 License Terms. **Following arbitration proceedings, the panel ruled in favor of each party on certain TAF associated claims and awarded** Ionis ~~claimed it was owed technology access fees, or TAFs, based on rights granted and amounts paid to us in connection with the Sanofi restructuring. Ionis later filed a Demand for Arbitration with the Boston office of the American Arbitration Association against us, asserting, among other things, breach of contract. Upon completion~~ **compensation** of **$ 41** ~~the arbitration process in the second quarter of 2020, in October 2020, a partial award was issued by the arbitration panel that sought additional information from us~~ . **2 million** ~~The arbitration panel issued its final award in December 2020, which ruled in favor of Ionis' s request~~ for a TAF on certain rights ~~the panel determined~~ we received in the Sanofi restructuring ~~(but rejected the TAF amount sought by Ionis), and in favor of us in denying Ionis' s request for a TAF on a milestone payment received by us in the same restructuring. The panel' s final award also denied Ionis' s request for pre-judgement interest and attorney' s fees. Pursuant to the panel' s final award, we paid $ 41. 2 million to Ionis in January 2021~~ . Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor' s rights. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of each of our approved products or future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in such products. Therefore, even if we successfully develop and commercialize products, we may be unable to ~~achieve or~~ maintain profitability. 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, potential** collaborators, employees, consultants, scientific advisors, CMOs, 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. In addition, other third parties may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. 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 business, prospects, operating results and financial condition. The pharmaceutical market is intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have: • substantially greater financial, technical and human resources than we have; • more extensive experience in ~~pre- clinical~~ **preclinical** testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling drug products; • product candidates that are based on previously tested or accepted technologies; • multiple products that have been approved or are in late stages of development; and • collaborative arrangements in our target markets with leading companies and research institutions. We ~~will~~ face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we ~~may~~ **have** ~~develop~~ **developed** ~~drugs~~ **products** . In addition, there are a number of drugs currently under development and that may become commercially available in the future, for the treatment of conditions for which we may try to develop ~~drugs~~ **product candidates** . These drugs may be more effective, safer, less expensive, have more convenient administration or be marketed and sold more effectively, than any products we develop and commercialize. For example, assuming ~~positive results in our HELIOS- B Phase 3 clinical and~~ regulatory approval, vutrisiran, our RNAi therapeutic in development for treatment of ATTR amyloidosis with cardiomyopathy, would compete with VYNDAQEL / VYNDAMAX (tafamidis), **which is** marketed by Pfizer, **and ATTRUBY (acoramidis),** which is **marketed by BridgeBio, both of which are** currently approved to treat ~~this disease. In addition, BridgeBio announced positive results from its Phase 3 clinical trial of acoramidis, a TTR stabilizer, in~~ ATTR amyloidosis with cardiomyopathy ~~in July 2023, and announced in February 2024 that the FDA has accepted its NDA for filing~~ . **We** ~~BridgeBio also announced that the European Medicines Agency has accepted its marketing authorization application and that it is preparing for additional global regulatory submissions. There~~ are also **aware of other** product candidates in **clinical** ~~earlier stages of~~ development for the treatment of ATTR amyloidosis with cardiomyopathy, including **WAINUA (eplontersen), which is being developed by Ionis and AstraZeneca plc, or AstraZeneca, and is in Phase 3 clinical development; nexiguran ziclumeran (formerly** NTLA- 2001 **),** which is being developed by Intellia Therapeutics, Inc. and Regeneron and is in Phase 3 clinical development; **ALN- 2220 (formerly NI006), which is being developed by Neurimmune AG and Alexion Pharmaceuticals, Inc. (a subsidiary of AstraZeneca) and is in Phase 3 clinical development; coramitug (** NNC- 6019 **- 0001),** which is being developed by Novo Nordisk and is in Phase ~~3~~ **2** clinical development; and ~~NI006~~ **AT0- 2,** which is being developed by **Attralus, Inc.** ~~Neurimmune AG and AstraZeneca plc~~ and is in Phase ~~1~~ **2** clinical development. We expect to face competition from any of these and potentially other additional new drugs that enter the market to treat patients with ATTR amyloidosis with cardiomyopathy. ONPATTRO and AMVUTTRA are approved in certain jurisdictions for the treatment of certain patients with hATTR amyloidosis with polyneuropathy. We are aware of other approved products used to treat this disease, including **WAINUA (eplontersen),** VYNDAQEL / VYNDAMAX (tafamidis), and TEGSEDI (inotersen), which is ~~developed and~~ marketed by Ionis. ~~In addition,~~ **There are also product candidates** in **various stages of clinical** ~~December 2023, the FDA approved WAINUA (eplontersen), a drug developed~~ **development** ~~by Ionis in partnership with AstraZeneca plc,~~ for the treatment of hATTR amyloidosis patients with polyneuropathy ~~. There are also product candidates~~ **, including ATO- 02, which is** in **Phase 2** ~~various stages of~~ clinical development ~~for the treatment of hATTR amyloidosis patients with polyneuropathy~~ **, and nexiguran ziclumeran (formerly NTLA- 2001), which is in Phase 1 clinical development** . While we believe that ONPATTRO and AMVUTTRA have and will continue to have a competitive product profile for the treatment of patients with hATTR amyloidosis with polyneuropathy, it is possible that ONPATTRO and / or AMVUTTRA may not compete favorably with these products and product candidates, or others, and, as a result, may not achieve commercial success. If we or our collaborators

continue to..... coverage; and • patent position. We are aware of **approved products and** product candidates in various stages of clinical development for the treatment of PH1 ~~which~~ **that** would compete with OXLUMO, our RNAi therapeutic approved in the U. S. and EU for the treatment of this disease, including Novo Nordisk' s ~~product~~ RIVFLOZA (nedosiran), which was approved for the treatment of PH1 in September 2023 and ~~is expected to launch~~ **launched** in **the U. S. in early** 2024. RIVFLOZA is a once- monthly subcutaneous RNAi therapy that was developed by Dicerna. In April 2020, we and Dicerna granted each other a non- exclusive cross- license to our respective intellectual property related to lumasiran and Dicerna' s nedosiran. In addition, several companies have investigational drugs in clinical development for the treatment of PH1, including ~~BridgeBio~~ **Biocodex** , ~~Chinook~~ **Inc. in collaboration with M8 Pharmaceuticals, Inc., and YolTech** Therapeutics ~~, Inc~~. **If we or our collaborators continue to successfully develop product candidates** , and ~~BioMarin Pharmaceutical~~ **obtain approval for them** , ~~Inc for them,~~ we and our collaborators will face competition based on many different factors,including:• the safety and effectiveness of our or our collaborators' products relative to alternative therapies,if any;• the ease with which our or our collaborators' products can be administered and the extent to which patients accept relatively new routes of administration;• the timing and scope of regulatory approvals for these products;• the availability and cost of manufacturing,marketing and sales capabilities;• the price of our or our collaborators' products relative to alternative approved therapies;• reimbursement coverage;and **• patent position** . Our competitors may develop or commercialize products with significant advantages over any products we or our collaborators develop based on any of the factors listed above or on other factors. In addition, our competitors may develop collaborations with or receive funding from larger pharmaceutical or biotechnology companies, providing them with an advantage over us and our collaborators. Our competitors may therefore be more successful in commercializing their products than we or our collaborators are, which could adversely affect our competitive position and business, prospects, operating results and financial condition. Competitive products may make any products we or our collaborators develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute on our business plan. Furthermore, we and our collaborators also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we and our collaborators are targeting could make our or our collaborators' product candidates noncompetitive, obsolete or uneconomical. We and our collaborators face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours, as well as from companies utilizing emerging technologies. If these companies develop drugs more rapidly than we or our collaborators do or their technologies, including delivery technologies, are more effective, our and our collaborators' ability to successfully commercialize our products may be adversely affected. In addition to the competition we face from competing drugs in general, we and our collaborators also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients with synthetic, exogenously- introduced genes designed to produce siRNA- like molecules within cells. Companies working on chemically synthesized siRNAs include, but are not limited to, Arrowhead and its collaborators, Takeda Pharmaceutical Company Ltd., Janssen Pharmaceutics, Inc., GlaxoSmithKline plc, and Amgen Inc.; Quark Pharmaceuticals, Inc.; Roche; Silence Therapeutics plc and its collaborators, AstraZeneca ~~plc~~ , Jiangsu Hansoh Pharmaceuticals Group Co., Ltd., and Mallinckrodt plc; Arbutus; Sylentis; ~~and~~ Novo Nordisk and its collaborators, **Aro Biotherapeutics Company,** Boehringer Ingelheim and Eli Lilly and Company **; and our collaborators Regeneron, Sanofi and Vir** . In addition, we granted licenses or options for licenses to Ionis, Benitec Biopharma Ltd., Arrowhead, Arbutus, Quark, Sylentis and other companies under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any one of these companies may develop its RNAi technology more rapidly and more effectively than we do. In addition, as a result of agreements that we have entered into, Takeda has obtained a non- exclusive license, and Arrowhead, as the assignee of Novartis, has obtained specific exclusive licenses for 30 gene targets, that include access to certain aspects of our technology. We and our collaborators also compete with companies working to develop antisense- based drugs. Similar to RNAi therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Akcea Therapeutics, Inc., a wholly owned subsidiary of Ionis, has received marketing approval for an antisense drug, inotersen for the treatment of adult hATTR amyloidosis patients with stage 1 or stage 2 polyneuropathy. Several antisense drugs developed by Ionis have been approved and are currently marketed **, including WAINUA (eplontersen)** , and Ionis has multiple antisense product candidates in clinical trials. Ionis is also developing antisense drugs using ligand- conjugated GalNAc technology licensed from us, and these drugs have been shown to have increased potency at lower doses in clinical and ~~pre- clinical~~ **preclinical** studies, compared with antisense drugs that do not use such licensed GalNAc technology. The development of antisense drugs and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes. In addition to competition with respect to RNAi and with respect to specific products, we face substantial competition to discover and develop safe and effective means to deliver siRNAs to the relevant cell and tissue types. If our competitors develop safe and effective means to deliver siRNAs to the relevant cell and tissue types, our ability to successfully commercialize a competitive product would be adversely affected. In addition, third parties are expending substantial resources to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, including both private companies and academic laboratories. Some of our competitors have substantially greater resources than we do, and if our competitors negotiate exclusive access to delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates. Our stock price has been and may in the future be volatile. From January 1, ~~2023~~ **2024** to December 31, ~~2023~~ **2024** , our common stock traded between $ ~~148~~ **141** . ~~10~~ **98** and $ ~~242~~ **304** . 39 per share. The stock market in general and the market for biotechnology companies in particular have experienced extreme price and volume volatility that

has often been unrelated to the operating performance of particular companies. The market price of our common stock in the future could be significantly and adversely affected by many factors, including: • the information contained in our quarterly earnings releases **and other public announcements** , including updates regarding our or our collaborators' commercialized products or product candidates, our net product and collaboration revenues and operating expenses for completed periods and financial guidance regarding future periods; • the success of existing or new competitive products or technologies; • regulatory actions with respect to our or our collaborators' products or product candidates; • announcements by us or our competitors of significant acquisitions, collaborations, joint ventures, collaborations or capital commitments; • the timing and results of clinical trials of our or our collaborators' other product candidates; • commencement or termination of collaborations for our development programs; • failure or discontinuation of any of our or our collaborators' development programs; • results of clinical trials of our competitors' product candidates; • regulatory or legal developments in the U. S. and other countries; • developments or disputes concerning patent applications, issued patents or other proprietary rights; • the recruitment or departure of key personnel; • the level of expenses related to any of our product candidates or clinical development programs; • the results of our or our collaborators' efforts to develop additional product candidates or products; • actual or anticipated changes in financial results or development timelines; • announcement or expectation of additional financing efforts; • sales of our common stock by us, our insiders or other stockholders; • variations in our financial results or those of companies that are perceived to be similar to us; • changes in estimates or recommendations by any of the securities analysts that cover us; • changes in the structure of healthcare payment systems; • market conditions in the pharmaceutical and biotechnology sectors; • general economic, industry and market conditions; and • the other factors described in this " Risk Factors " section. In the past, securities class action litigation has often been brought against companies following declines in the market price of their securities. This risk is especially relevant for biopharmaceutical companies, which have experienced significant stock price volatility in recent years. **We may be** ~~For example, in September 2019, we and certain of our current and former directors and officers, and~~ the ~~underwriters~~ **target** of ~~our November 2017 stock offering were sued in a putative class action alleging violations of the federal~~ securities ~~laws. While this matter has been finally settled, we may be the target of additional~~ litigation **that** ~~of this type in the future. Securities litigation against us~~ could result in substantial costs and divert our management' s attention and resources, which could cause serious harm to our business, prospects, operating results and financial condition. We maintain liability insurance; however, if any costs or expenses associated with litigation exceed our insurance coverage, we may be forced to bear some or all of these costs and expenses directly, which could be substantial. In addition, we have obligations to indemnify third parties, including our officers and directors ~~and underwriters of our securities offerings~~ , in connection with certain litigation, and those obligations may not be covered by insurance. Sales of a substantial number of shares of our common stock, including by us, our officers or directors, or our significant stockholders, into the public market could cause the price of our common stock to decline. A small number of our stockholders beneficially own a substantial amount of our common stock. As of December 31, ~~2023~~ **2024** , our ~~seven~~ **eight** largest stockholders beneficially owned in excess of 50 % of our outstanding shares of common stock. If we, our officers or directors, or our significant stockholders sell substantial amounts of our common stock in the public market, or there is a perception that such sales may occur, the market price of our common stock could be adversely affected. Sales of common stock by our significant stockholders might make it more difficult for us to raise funds by selling equity or equity- related securities in the future at a time and price that we deem appropriate. Anti- takeover provisions in our governing documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management or members of our board of directors. Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in the current members of our management or the members of our board of directors. Among other things, these provisions: • establish a classified board of directors such that all members of our board of directors are not elected at one time; • establish a prohibition on actions by our stockholders by written consent; • authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a " poison pill " that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; • allow the authorized number of our directors to be changed only by resolution of our board of directors. • limit who may call a special ~~meetings~~ **meeting** of stockholders; • require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to ~~case~~ **cast** to amend or repeal certain provisions of our charter or bylaws; • limit the manner in which stockholders can remove directors from our board of directors; and • establish advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders. Any new information regarding our and our collaborators' products and product candidates or competitive products or potentially competitive product candidates can substantially affect investors' perceptions regarding our future prospects. We, our collaborators, and our competitors periodically provide updates regarding drug development programs, typically through press releases, conference calls and presentations at medical conferences. These periodic updates often include interim or final results from clinical trials conducted by us or our competitors and / or information about our or our competitors' expectations regarding regulatory filings and submissions as well as future clinical development of our products or product candidates, competitive products or potentially competitive product candidates. The timing of the release of information by us regarding our drug development programs is often beyond our control and is influenced by the timing of receipt of data from our clinical trials and by the general preference among pharmaceutical companies to disclose clinical data during medical conferences. In addition, the information disclosed about our clinical trials,

or our competitors' clinical trials, may be based on interim rather than final data that may involve interpretation difficulties and may in any event not accurately predict final results. The release of such information may result in volatility in the price of our common stock. For example, in late 2021 our stock price was negatively impacted following BridgeBio' s public disclosure of the results of Part A of the Phase 3 clinical trial of acoramidis for the treatment of ATTR amyloidosis with cardiomyopathy. As of December 31, ~~2023~~ **2024** , we had $ 1. ~~02~~ **04** billion in **total** aggregate principal amount of Notes **issued and** outstanding. The interest rate for the Notes is fixed at 1. 00 % per annum and is payable semi- annually in arrears on ~~May~~ **March** 15 and September 15 of each year, beginning on March 15, 2023. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance our indebtedness, including the Notes, or to make cash payments in connection with any conversions of Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt and make necessary capital expenditures. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional debt financing or equity capital on terms that may be onerous or highly dilutive. Our ability to refinance any future 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. In addition, our indebtedness, combined with our other financial obligations and contractual commitments, could have other important consequences. For example, it could: • make us more vulnerable to adverse changes in general U. S. and worldwide economic, industry and competitive conditions and adverse changes in government regulation; • limit our flexibility in planning for, or reacting to, changes in our business and our industry; • place us at a disadvantage compared to our competitors who have less debt; • limit our ability to borrow additional amounts to fund acquisitions, for working capital and for other general corporate purposes; and • make an acquisition of our company less attractive or more difficult. Any of these factors could harm our business, prospects, operating results and financial condition. In addition, if we incur additional indebtedness, the risks related to our business and our ability to service or repay our indebtedness would increase **. We may not have the ability to raise the funds necessary to settle for cash conversions of the Notes or to repurchase the Notes for cash upon a fundamental change** . Holders of the Notes have the right to require us to repurchase their Notes upon the occurrence of a fundamental change (as defined in the indenture governing the Notes) at a repurchase price equal to 100 % of the principal amount of the Notes to be repurchased, plus accrued and unpaid interest, if any. Upon conversion of the Notes, unless we elect to deliver solely shares of our common stock to settle such conversion (other than paying cash in lieu of delivering any fractional share), we will be required to make cash payments in respect of the Notes being converted. We may not have enough available cash or be able to obtain financing at the time we are required to make repurchases of Notes surrendered or Notes being converted. In addition, our ability to repurchase the Notes or to pay cash upon conversions of the Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase Notes at a time when the repurchase is required by the indenture governing such notes or to pay any cash payable on future conversions of the Notes as required by such indenture would constitute a default under such indenture. A default under the indenture governing the Notes or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the Notes or make cash payments upon conversions. In the event the conditional conversion feature of the Notes is triggered, holders of the Notes will be entitled to convert the Notes at any time during specified periods at their option. If one or more holders elect to convert their Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock (other than paying cash in lieu of delivering any fractional share), we would be required to settle a portion or all of our conversion obligation through the payment of cash, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the Notes as a current liability, rather than long- term liability, which would result in a material reduction of our net working capital. Transactions relating to the Notes may affect the value of our common stock. The conversion of some or all of the Notes would dilute the ownership interests of existing stockholders to the extent we satisfy our conversion obligation by delivering shares of our common stock upon any conversion of such Notes. The Notes may become in the future convertible at the option of their holders under certain circumstances. If holders of the Notes elect to convert their notes, we may settle our conversion obligation by delivering to them a significant number of shares of our common stock, which would cause dilution to our existing stockholders. In addition, in connection with the issuance of the Notes, we entered into the Capped Calls with certain financial institutions, or the Option Counterparties. The Capped Calls are generally expected to reduce potential dilution to our common stock upon any conversion or settlement of the Notes and / or offset any cash payments we are required to make in excess of the principal amount of converted Notes, with such reduction and / or offset subject to a cap. In connection with establishing their initial hedges of the Capped Calls, the Option Counterparties or their respective affiliates entered into various derivative transactions with respect to our common stock and / or purchased shares of our common stock concurrently with or shortly after the pricing of the Notes. From time to time, the Option Counterparties or their respective affiliates may modify their hedge positions by entering into or unwinding various derivative transactions with respect to our common stock and / or purchasing or selling our common stock or other securities of ours in secondary market transactions prior to the maturity of the Notes (and are likely to do so following any conversion of the Notes, any repurchase of the Notes by us on any fundamental change repurchase date, any redemption date, or any other date on which the Notes are retired by us, in each case, if we exercise our option to terminate the relevant portion of the Capped Calls). This activity could cause a decrease and / or increased volatility in the market price of our common stock. We do not make any representation or prediction as to the direction or magnitude of any potential effect that the transactions described above may have on the price of the Notes or our common stock. In addition, we do not make any representation that the Option Counterparties will engage in these transactions or that these transactions, once

commenced, will not be discontinued without notice. We are subject to counterparty risk with respect to the Capped Calls. The Option Counterparties are financial institutions, and **are** ~~we will be~~ subject to the risk that any or all of them might default under the Capped Calls. Our exposure to the credit risk of the Option Counterparties will not be secured by any collateral. Past global economic conditions have resulted in the actual or perceived failure or financial difficulties of many financial institutions. If an Option Counterparty becomes subject to insolvency proceedings, we will become an unsecured creditor in those proceedings with a claim equal to our exposure at that time under the Capped Calls with such Option Counterparty. Our exposure will depend on many factors but, generally, an increase in our exposure will be correlated to an increase in the market price and in the volatility of our common stock. In addition, upon a default by an Option Counterparty, we may suffer adverse tax consequences and more dilution than we currently anticipate with respect to our common stock. We can provide no assurances as to the financial stability or viability of the Option Counterparties. The accounting method for convertible debt securities that may be settled in cash, such as the Notes, could have a material effect on our reported financial results. The accounting method for reflecting the Notes on our consolidated balance sheet, accruing interest expense for the Notes and reflecting the underlying shares of our common stock in our reported diluted earnings per share may adversely affect our reported earnings and financial condition. **The** ~~In August 2020, the Financial Accounting Standards Board published an Accounting Standards Update, which we refer to as ASU 2020- 06, which simplified certain of the accounting standards that apply to convertible notes. ASU 2020- 06 became effective for us beginning January 1, 2022. In accordance with ASU 2020- 06, the~~ Notes are reflected as a liability on our consolidated balance sheets, with the initial carrying amount equal to the principal amount of the Notes, net of issuance costs. The issuance costs were treated as a debt discount for accounting purposes, which is being amortized into interest expense over the term of the Notes. As a result of this amortization, the interest expense that we expect to recognize for the Notes for accounting purposes will be greater than the cash interest payments we will pay on the Notes, which will result in lower reported net income or higher reported net loss, as the case may be. In addition, the shares of common stock underlying the Notes are reflected in our diluted earnings per share using the " if **-** converted " method, in accordance with ASU 2020- 06. Under this method, diluted earnings per share is generally calculated assuming that all the Notes were converted solely into shares of common stock at the beginning of the reporting period, unless the result would be anti- dilutive. The application of the if- converted method may reduce our reported diluted earnings per share to the extent we are profitable in the future, and accounting standards may change in the future in a manner that may adversely affect our diluted earnings per share. Furthermore, if any of the conditions to the convertibility of the Notes is satisfied, then we may be required under applicable accounting standards to reclassify the liability carrying value of the Notes as a current, rather than a long- term, liability. This reclassification could be required even if no holders actually convert their Notes and could materially reduce our reported working capital.