Risk Factors Comparison 2024-02-15 to 2023-02-23 Form: 10-K

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

Investing ~~We operate~~ in **our securities** ~~an environment that~~ involves a ~~number~~ **high degree** of ~~significant risks~~ **risk** ~~and uncertainties~~. **You should carefully consider** ~~We caution you to read~~ 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** ~~which have affected, and / or~~ **our** ~~in~~ **consolidated financial statements and** the ~~future could affect~~ **related notes and " Management' s Discussion of Financial Condition and Results of Operations**, **" in evaluating our company and** our business ~~, prospects, operating results, and financial condition~~. ~~The~~ **If any of the following** risks ~~described below include forward- looking statements~~, ~~and actual events and our~~ **or any** ~~actual results may differ materially from these forward- looking statements. Additional~~ **additional** ~~risks~~ **risk** ~~and uncertainties~~ not currently known to us or that we currently deem immaterial ~~may also impair~~ **, actually occurs,** our business, prospects, operating ~~results~~ **result or** ~~, and~~ financial condition **could** ~~. Furthermore, additional risks and uncertainties are described under other captions in this report and should also~~ be ~~considered by~~ **materially and adversely affected. In these circumstances, the trading price of our common stock could decline, and you may lose all or part of** ~~our~~ **your** ~~investors~~ **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 ~~ONPATTRO and~~ AMVUTTRA. • We have a history of losses and may never become and remain ~~consistently~~ profitable. • We will require substantial funds to continue our research, development and commercialization activities. • **Any** ~~The current pandemic of COVID- 19 and its variants and the future outbreak of other highly infectious or contagious diseases, could continue to have an adverse impact on our business, financial condition and results of operations, including our commercial operations and sales, clinical trials and pre- clinical studies, and could impact other areas of our business as well. • Although we sold a portion of the expected royalty stream and commercial milestones related to global sales of Leqvio by Novartis, we are entitled to retain the remaining portion of such future royalties and, if certain specified thresholds are met, to the remaining portion of commercial milestone payments, and any~~ negative developments related to Leqvio could have a material adverse effect on ~~the timing or~~ **our** ~~amount~~ **receipt** of ~~those~~ **future royalties and milestone** payments. Risks Related to Our Dependence on Third Parties • We may ~~not~~ be ~~able to execute our business strategy if we are~~ unable to maintain existing or enter into new ~~alliances~~ **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 ~~and we could suffer other economic harm~~. • We ~~have limited~~ **expect to continue to grow our** manufacturing ~~experience~~ **capabilities** and resources ~~,~~ and we must incur significant costs to develop this expertise and / or rely on third parties to manufacture our products. • We rely on third parties to conduct our clinical trials, and if ~~they~~ **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 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 ~~candidates~~ **candidate** we ~~or our~~ **or** ~~partners~~ **our collaborators** develop may fail in development or be delayed to a point where ~~they do~~ **such product candidate does** not become commercially viable. • We or our ~~partners~~ **collaborators** may be unable to obtain U. S. or foreign regulatory approval for our or our ~~partnered~~ **collaborated** product candidates, **and** ~~or if approved~~, **as a result, we** ~~may fail to obtain desired labeling for~~ **or our collaborators may be unable to commercialize** such ~~products~~ **product candidates**. • Even if we or our ~~partners~~ **collaborators** obtain regulatory approvals, our **products** ~~marketed drugs~~ 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 ~~receive regulatory approval to market our~~ **or** ~~product candidates, and~~ our collaborators receive regulatory approval to market **our** product candidates ~~discovered by us or developed with our technology~~, 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 ~~scale~~ **build** our marketing, sales, market access and distribution capabilities and further establish our global ~~commercial and compliance~~ infrastructure, and our ~~commercial~~ efforts may not be successful. • ~~We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities or promoting our commercially approved products in a way that violates applicable regulations, including in connection with the ongoing DOJ investigation. •~~ Any drugs 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~~ 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. 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 ~~, including gene therapy and gene editing~~. Risks Related to Our Common Stock • **Our** ~~If our~~ stock price ~~fluctuates~~ **has been and may in the future be volatile** . ~~purchasers of~~ **and an investment in** our common stock could ~~incur substantial losses~~ **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 ~~incur~~ **result in** significant **volatility in the price** ~~costs from class action litigation. • Future sales of shares~~ of our common stock ~~, including by our significant stockholders, us or our directors and officers, could cause the price of our common stock to decline~~. Risks Related to Our Convertible Notes • ~~Servicing our debt may require a significant amount of cash.~~ 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 Notes or to repurchase the Notes for cash upon a fundamental change ~~, and our future debt may contain limitations on our ability to pay cash upon conversion of the Notes or to repurchase the Notes~~. • The conditional conversion feature of the Notes, if triggered, may adversely affect our **liquidity** ~~financial condition and operating results~~. 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 ~~ONPATTRO and~~ **certain of our commercial products, including** AMVUTTRA. **Although** ~~In 2018, our first commercial product, ONPATTRO, was approved by the FDA and EMA, and we have since received approval and launched ONPATTRO in several additional territories. In 2019, the FDA approved our second product, GIVLAARI, which was also approved by the EMA and has since received approval in several additional territories, and in 2020, the FDA and EMA approved our third product, OXLUMO, which received additional regulatory approvals in 2021 and 2022. In June 2022, the FDA approved AMVUTTRA, which was granted marketing authorization in Europe and the UK in September 2022 and has since received regulatory approval in Japan and Brazil. We also have multiple product candidates in late- stage clinical development. While~~ we have commercially launched four products, we cannot predict whether we will successfully market and sell our approved products, or successfully expand the **approved** indications of certain of our ~~approved~~ **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 APOLLO- B results after 12 months validate the therapeutic hypothesis of RNAi therapeutics targeting TTR as potential treatment for patients with ATTR amyloidosis with cardiomyopathy ~~and submitted an~~ **, in October 2023, the FDA issued a CRL for our** sNDA ~~to the FDA~~ for ~~review in December 2022, we cannot be certain that the results from the APOLLO- B clinical trial will support regulatory approval of~~ patisiran for the treatment of ~~patients with~~ 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 ~~over~~ **by** the ~~next 5 years~~ **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 ~~success for~~ our approved products, as well as any other products we commercialize; • attract and retain customers for our products; • ~~develop~~ **enter into** and maintain successful **collaborations** ~~strategic alliances~~ ; and • manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization. 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, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~6~~ **7** . ~~57~~ **01** 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 ~~2023~~ **2024** and beyond, we may never attain profitability or positive cash flow from operations. For the year ended December 31, ~~2022~~ **2023** , we recognized $ ~~894~~ **1** . ~~3~~ **24** ~~million~~ **billion** in net product revenues from sales of ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO. 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 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 ~~current alliances~~ **existing collaborations**, including milestones and royalties on Leqvio sales, should enable us to achieve a self- sustainable profile 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 ~~alliances~~ **collaborations** with pharmaceutical and biotechnology companies, including **Roche,** Novartis ~~and~~ **,** Regeneron **, Sanofi and Vir**. We cannot be certain that we will be able to maintain our existing ~~alliances~~ **collaborations**, secure and maintain new ~~alliances~~ **collaborations**, meet ~~the~~ **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 ~~alliances~~ **collaborations**. Moreover, we cannot be certain that our ~~partners~~ **collaborators**, including Novartis, will continue to successfully execute their obligations under our ~~alliance~~ **collaboration** agreements and generate ~~additional~~ **collaboration and royalty** revenues for us. **To** ~~We believe that to~~ become and remain ~~consistently~~ profitable, we must succeed in discovering, developing and commercializing novel ~~drugs~~ **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 testing and clinical trial stages of development, obtaining regulatory approval and reimbursement for ~~these~~ **our** novel ~~drugs~~ **product candidates** and manufacturing, marketing and selling ~~them~~ **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 additional product candidates or continue our operations. We will require substantial funds to continue our research, development and commercialization activities **,** and if ~~the~~ **we require greater** funds ~~we require are greater~~ than ~~what~~ we have estimated, we may need to critically limit ~~or~~ **,** significantly scale back or cease certain ~~of our~~ 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 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 ~~, including zilebesiran,~~ may be greater than we anticipate, we are unable to estimate the actual funds **needed** ~~we will require~~ to develop and commercialize ~~them~~ **our product candidates**. 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 ~~alliances~~ **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. ~~However~~ **Nevertheless**, our future capital requirements and the period for which ~~we expect~~ our existing resources ~~to~~ **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 diseases as well as what may be required by regulatory ~~bodies~~ **authorities** to advance these programs; • the timing, receipt and amount of milestone **, royalty** and other payments, if any, from present and future collaborators, if any, including milestone **and royalty** 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 ~~, which is being commercialized by our partner, Novartis~~; • our ability to maintain and establish additional ~~collaborative~~ **collaborations** ~~arrangements~~ 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- clinical 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 products for** commercial sale; • the impact of ~~COVID- 19~~ **any future pandemics or public health emergencies** or the ongoing ~~conflict~~ **conflicts** in **the Middle East and** Ukraine on the initiation or completion of pre- clinical 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, if and when approved; and • the outcome of the regulatory review process and commercial success of ~~drug~~ products for which we are entitled to receive royalties, including Leqvio. 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 ~~additional~~ **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. The COVID- 19 pandemic and its..... experience delays in their regulatory activities. Although we sold a portion of the royalty stream and commercial milestones from the global sales of Leqvio by ~~our collaborator,~~ Novartis, we are entitled to retain the remaining ~~portion~~ **portions** of **the** future royalties ~~from the global sales of Leqvio~~ and ~~, if certain specified thresholds are met, to the remaining portion of~~ 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 Blackstone 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 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' s **interest in Leqvio** ~~royalty~~ **royalties will increase to 55 % (and our** interest will ~~increase~~ **decrease** to ~~55~~ **45** % **)** effective January 1, 2030. ~~Our receipt~~ **As a result, any factor that has an adverse impact on sales** of ~~future royalty~~ **Leqvio could affect our ability to meet the $ 1. 00 billion** ~~payments~~ -- **repayment** ~~and~~ **threshold in this timeframe, which in turn would have** a ~~portion of commercial milestone payments may be negatively~~ -- **negative** ~~impacted~~ -- **impact** ~~if~~ **on the percentage of** the Leqvio royalty stream **that we** ~~and commercial milestones payments~~ are ~~insufficient~~ **entitled** to **retain** ~~meet the specified thresholds~~ . **Factors** ~~For example, in December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating~~ that ~~the agency~~ could ~~not approve the NDA by the PDUFA action date due to unresolved inspection- related conditions at a third party manufacturing facility, delaying the potential approval and launch of Leqvio in the U. S., as well as payment of an associated approval milestone and potential royalties. While Leqvio was granted marketing authorization by the EC in Europe in December 2020, and was approved by the FDA in December 2021, any negative impact to future royalty payments and commercial milestone payments could affect our ability to meet the specified repayment thresholds. Additional factors that may~~ have an adverse ~~effect~~ **impact** on ~~the~~ Leqvio **sales** ~~royalty stream and commercial milestones~~ include: • companies working to develop new therapies or alternative formulations of products for ASCVD; • **lack of acceptance** ~~foreign currency movement, which could have a negative impact on Novartis' sales~~ of Leqvio **by patients** , ~~thereby reducing~~ the ~~royalties~~ **medical community or third party payors** ; • any negative developments relating to Leqvio, such as safety, efficacy, or reimbursement issues ~~, could reduce demand for Leqvio~~ ; • any disputes concerning patents ~~,~~ **or** proprietary rights, or **under** license and collaboration agreements **; • foreign currency exchange rate fluctuations** ~~could negatively impact our receipt of commercial milestone payments or royalties~~ ; and • adverse regulatory or legislative developments ~~could~~ **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 ~~, which may significantly reduce expected royalty revenue and commercial milestone payments and could require significant expense to address the associated legal and regulatory issues~~ . 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 ~~and results of operations~~ , 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 financial markets and the global economy~~ . The uncertain nature, magnitude, and duration of hostilities stemming from the conflict in Ukraine, including the potential effects of sanctions ~~limitations,~~ retaliatory cyber- attacks on the world economy and markets, have ~~also~~ 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 ~~may~~ **has** ~~disrupt~~ **disrupted** the ability **of certain** of our contract research organizations, or CROs, to conduct clinical trials at certain sites in Ukraine. ~~Moreover, enrollment and retention of clinical trial participants may be adversely affected.~~ 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. ~~We expect our operating results to fluctuate in future periods, which may adversely affect our stock price. Our quarterly operating results have fluctuated in the past, and may continue to do so in the future. Our operating results may fluctuate due to the impact of the COVID- 19 and related variants or a future pandemic, the level of success of our commercial efforts and resulting revenues, as well as the variable nature of our operating expenses as a result of the timing and magnitude of expenditures. For example, due to the impact of the COVID- 19 pandemic, combined net product revenues in the first quarter of 2022 for our commercially approved products were negatively impacted. In addition, in one or more future periods, our results of operations may fall below the expectations of securities analysts and investors. In that event, the market price of our common stock could substantially decline.~~ If the estimates we make, or the assumptions on which we rely, in preparing our ~~consolidated~~ 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, ~~2022~~ **2023** , we had $ 2. ~~19~~ **44** 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, which is focused on the preservation of our capital. 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 ~~consolidated~~ financial ~~statements~~ **condition** . In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would ~~suffer~~ **decline** . The market risks associated with our investment portfolio may have an adverse effect on our **operating** results ~~of operations~~ , 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. ~~will~~ **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. 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 ~~law~~ **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** ~~cash flow~~ , **operating results and** financial condition ~~or results of operations~~ . 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, ~~the~~ 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 successfully commercialize our approved products, and we** may not be able to ~~including our ability to 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 ~~the current or~~ 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 ~~partners~~ **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 activities and initiation of planned clinical trials are dependent upon the availability of,for example,pre- clinical 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 ~~ongoing~~ 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 ~~continue to~~ **may again** be affected by COVID- 19,and ~~believe that~~ **any resurgence of** the COVID- 19 pandemic **and its variants** could ~~continue to~~ have an impact on various aspects of our ongoing clinical trials and on the clinical trials and pre- clinical studies we ~~execute~~ -- **expect to initiate during 2024** ~~and other important agencies and contractors,which could adversely impact the clinical trials of our product candidates~~ .Health regulatory agencies globally may also experience disruptions in their operations ~~if the conditions~~ **as a result** of the COVID- 19 pandemic ~~worsen~~ **or future public health emergencies** ,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. ~~For example~~ **While the ultimate impact of COVID- 19** , ~~in December 2020~~ **or any future pandemic or public health emergency** , **on** ~~the FDA~~ our business ~~strategy if~~ **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 ~~alliances~~ **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** ~~. If we are unsuccessful in forming or maintaining these alliances~~ on ~~terms favorable to us,~~ our business ~~may~~ **, prospects, operating results and financial condition. We do** not **currently** ~~succeed. We are continuing to advance our commercial capabilities, including in marketing, sales, market access and distribution, to support our wholly- owned products. We also continue to advance our growing pipeline of RNAi therapeutic opportunities. However, we may not~~ have adequate capacity or capabilities to advance all ~~of our therapeutic~~ opportunities **arising from our growing pipeline of RNAi therapeutics** . Accordingly, we have entered into ~~alliances~~ **collaborations** with **third party** ~~other companies and~~ collaborators ~~that~~ 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 ~~alliances~~ **collaborations** in the future. ~~Our collaboration strategy is to form alliances that create significant value for us and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines.~~ Specifically, **we currently have active collaborations** with ~~respect to our Genetic Medicine pipeline~~ , **among others,** ~~as a result of our broad strategic alliance with~~ Sanofi ~~formed in 2014~~ , ~~Sanofi has the right to develop and commercialize fitusiran globally. In addition, we formed a collaboration with MDCO (which was acquired by~~ Novartis ~~in January 2020) to advance inclisiran. In March 2018~~ , ~~we entered into a discovery collaboration with~~ Regeneron ~~to identify RNAi therapeutics for NASH and potentially other related diseases~~ , **Vir** ~~and in November 2018~~ , ~~we~~ **Novo Nordisk** and **Roche covering various products** ~~Regeneron entered into a separate, fifty- fifty collaboration to further research, co- develop~~ and ~~commercialize any therapeutic~~ product candidates ~~that emerge from these discovery efforts. In October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection. In April 2020, we entered into a development and commercialization collaboration with Dicerna (which was acquired by Novo Nordisk~~ in ~~December 2021) to advance investigational RNAi therapeutics for the treatment of alpha- 1 liver disease. With respect to~~ our ~~CNS / Ocular Disease~~ pipeline ~~, in April 2019, we announced a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver~~ . In such ~~alliances~~ **collaborations** , we expect our current, and may expect our future, collaborators to provide substantial capabilities in clinical development, regulatory affairs, and / or marketing, sales and distribution. Under certain of our ~~alliances~~ **collaborations** , we also ~~may~~ expect our collaborators to develop, market and / or sell certain of our product candidates ~~. We may~~ **, in certain territories or globally, and we** have limited or no control over the development, sales, marketing and distribution activities of these **collaborators** ~~third parties~~ . 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** ~~all future~~ development and commercialization of Leqvio worldwide **;** ~~, and~~ (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 ~~such~~ collaboration referenced in clauses (i)- (~~iii~~ **iv**) above, we are entitled to royalties **, and in some instances commercial milestone payments,** on the sales of ~~each of these~~ -- **the applicable** ~~products~~ **product** . If our collaborators are not successful in their development and / or commercialization efforts, our future revenues from ~~RNAi therapeutics~~ **the relevant product** ~~for~~ **or** ~~these indications~~ **product candidate** may be adversely affected. For example, ~~while Leqvio was granted marketing authorization by the EC in Europe,~~ in December 2020 ~~,~~ Novartis received a complete response letter from the FDA stating that the ~~agency~~ **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 complete response letter resulted in a delay in the payment of an approval milestone and potential U. S. royalties. ~~If~~ **As discussed above, under our agreement with Blackstone, if** the revenues generated by the royalties received by Blackstone from us with respect to Leqvio sales do not reach a certain level by the end of 2029, Blackstone 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 ~~alliances~~ **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 ~~and GEMINI platforms~~ **platform**, our ability to successfully demonstrate proof- of- concept for our technology in humans in certain tissues or disease areas, ~~including our alternative conjugate approach for delivering CNS or~~ **our** ~~ocular~~ **ability to demonstrate the safety and efficacy of our specific** product ~~candidates or other extrahepatic approaches, our ability to demonstrate the safety and efficacy of our specific drug~~ 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** ~~. For example, the occurrence of a fatal thrombotic serious adverse event, or SAE, in our fitusiran study in 2017 and a subsequent pause in dosing and enrollment in fitusiran clinical studies in 2020 could contribute to further concerns about the safety of specific therapeutic candidates or therapeutic candidates for specific diseases~~. Even when we succeed in securing such ~~alliances~~ **new collaborations**, we may not be able to maintain them 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 ~~or~~ **,** sales of an approved drug are lower than we expected **, or our collaborator changes its strategic focus**. Furthermore, any delay in entering into **new** collaboration agreements would ~~likely either~~ **have the potential to prevent or** delay the development and commercialization ~~of certain of our product candidates and reduce their competitiveness even if they reach the market, or prevent the development~~ of certain product candidates ~~. Any~~ **, or reduce the competitiveness** such ~~delay related to our collaborations~~ **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 Regeneron **, Roche**, 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 ~~agreement~~ **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, or to bring ~~our~~ **such** product candidates to market. **In these circumstances** ~~If we do not have sufficient funds to develop and bring our product candidates to market~~, 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 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 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 or a particular program under the collaboration, under certain circumstances. For example, our agreement with ~~MDCO, which was acquired by~~ Novartis ~~in January 2020,~~ 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 ~~of our~~ 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~~ **Agreement** or disputes with Novartis regarding ~~each party' s rights and obligations under~~ the MDCO **License** ~~agreement~~ **Agreement** could adversely impact our ability to comply with our obligations under our agreements with Blackstone. 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 ~~RNAi therapeutics~~ **the affected product or product candidate**, it could delay our development of product candidates, result in the need for additional company resources to develop 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 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 have ~~limited~~ **been expanding our** manufacturing ~~experience~~ **capabilities,** and ~~resources and we must incur significant costs to develop this expertise and / or rely on third parties to manufacture our products. We have limited manufacturing experience. 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 ~~for,~~ or otherwise arrange for ~~the~~ **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 ~~that is~~ **and such material was** not required to be produced under ~~GMP~~ **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 ~~substance~~ **substances** for ~~clinical and, eventually, will manufacture for commercial use. In December 2020, we began cGMP operations, and we believe this facility will enable us to initiate manufacturing for multiple new~~ early- stage ~~programs over~~ **clinical development and have** the **possibility to** ~~next few years, as well as provide us the manufacturing~~ **manufacture drug substances for** ~~capabilities to support our~~ late- stage **clinical development** and commercial ~~programs~~ **use,** in the future. At the present time, we ~~may~~ **only have the capacity to** manufacture limited quantities of clinical trial ~~materials~~ **drug substance** ourselves, ~~but~~ **and** otherwise we continue to rely on third ~~parties~~ **party CMOs** to manufacture ~~the~~ **additional** drug substance **,** and ~~finished~~ **we rely on third party CMOs for all of our drug** product **requirements** ~~we will require~~ for clinical ~~trials that we initiate~~ and ~~to support the~~ commercial **use** ~~supply of our approved products and any of our other product candidates~~ . There are a limited number of **CMOs worldwide with the expertise to** ~~manufacturers~~ -- **manufacture our** ~~that supply synthetic siRNAs~~ **siRNA** ~~. We~~ **therapeutic products, and we** currently rely on a limited number of **North American and European** CMOs ~~for~~ **to manufacture** our ~~supply of synthetic siRNAs~~ **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 ~~ultimately~~ **if our CMOs fail to do these things it could** delay our clinical trials and potentially put **our commercial supply** at risk ~~commercial supply~~ , as well as result in additional expense to us. To fulfill our ~~siRNA~~ **future** requirements, we will likely need to **contract with additional CMOs,** ~~secure alternative suppliers of synthetic siRNAs~~ and such alternative suppliers ~~are~~ **may be** limited **,** ~~and may~~ not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner ~~. As noted above~~ , ~~in order to ensure long- term supply capabilities for~~ **or at all** ~~our RNAi therapeutics, we are developing our own capabilities to manufacture drug substance for clinical and commercial use~~ . In addition to the manufacture of ~~the~~ 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 ~~very~~ 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 cause delays in our discovery and development efforts, as well as additional expense to us. In ~~response to the COVID- 19 pandemic, in March 2020, the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, was enacted in March 2020, and requires that manufacturers have in place a risk management plan that identifies and evaluates the risks to the supply of approved drugs for certain serious diseases or conditions for each establishment where the drug or active pharmaceutical ingredient is manufactured. The risk management plan will be subject to FDA review during an inspection. If we experience shortages in the supply of our marketed products, as a result of COVID- 19 or otherwise, our results could be materially impacted. 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 ~~our dependence on~~ **the ongoing utilization of** our own ~~facility~~ **facilities** , any delay ~~in supply caused by the COVID- 19 pandemic could impact our ability to procure sufficient supplies for our approved products, and the development of our product candidates could also be delayed. Any delay~~ or setback in the manufacture of our ~~approved~~ products could impede ongoing **clinical and** commercial supply, which could ~~significantly~~ **materially and adversely** impact our ~~revenues and~~ **business, prospects,** operating results **or financial condition** . In addition, to the extent we or our ~~partners~~ **collaborators** rely on CMOs ~~outside of the U. S.~~ to supply ~~drug substance for~~ our product candidates, any delays or disruptions in supply ~~caused by the COVID- 19 pandemic~~ could have a material adverse impact on the research and development activities and potential commercialization of our or our ~~partners'~~ **collaborators'** product candidates. The manufacturing ~~process~~ **processes** for our ~~approved~~ products and any other ~~products~~ **product candidates** that we may develop ~~,~~ is subject to the FDA and foreign regulatory authority approval process 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 ~~existing regulatory~~ **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 ~~for vutrisiran~~. 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. 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 ~~in supply~~; • 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, 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 ~~certain~~ **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 ~~all of~~ 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, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, ~~the~~ EMA, ~~the~~ PMDA ~~in Japan~~ or ~~comparable~~ **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. If our third- party service providers cannot adequately and timely fulfill their obligations to us for any reason, ~~including due to disruptions caused by the COVID- 19 pandemic or the ongoing conflict in Ukraine on their operations or at the sites they are overseeing,~~ or if the quality and accuracy of our clinical trial data is compromised due to failure by such third party **service provider** to adhere to our protocols or regulatory requirements or if such third ~~parties~~ **party service providers** otherwise fail 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 ~~, and our results of operations and~~ **. Before conducting clinical trials to demonstrate** the ~~commercial prospects for~~ **safety and efficacy of** our product candidates ~~would~~ **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 ~~harmed,~~ **unable to complete such pre- clinical studies in a timely manner** ~~our~~ **or** ~~costs~~ **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 ~~increase~~ **be impaired** and our ~~ability to generate additional revenues~~ **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 ~~of the~~ 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 ~~with which~~ to attract and reward qualified individuals than we do. In addition, if we are not successful **in** commercializing our approved products, we may be unable to attract and retain

highly qualified sales and marketing professionals **, and if we are not able** to ~~support~~ **attract and retain qualified sales and marketing professionals, it would negatively impact our ability to commercialize** our approved products and ~~our~~ **any** future products ~~, if approved~~ . Accordingly, we may be unable to attract and retain suitably qualified individuals ~~in order~~ to support our growing research, development and global commercialization efforts and initiatives, and our failure to do so could 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 testing and clinical development into a global company that develops and commercializes multiple ~~drugs~~ **products** . 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., ~~the~~ 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. Social media is being used to communicate about our clinical development programs and the diseases our investigational RNAi therapeutics are being developed to treat, and we are utilizing what we believe is appropriate social media in connection with our commercialization efforts for our approved products, and we intend to do the same for our future products, if approved. 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 or to report an alleged **adverse event, or** AE. When such disclosures occur, there is a risk that study enrollment may be adversely impacted, we fail to monitor and comply with applicable AE reporting obligations or that we may not be able to defend our business ~~or the public' s legitimate interests~~ 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 we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions or incur 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** ~~an attractive target of~~ criminal attack or unauthorized access and use by third parties with a wide range of motives and expertise, including organized criminal groups, " hacktivists, " patient groups, disgruntled current or former employees and others. 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 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 ~~and~~ **,** 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** ~~(including COVID- 19)~~ , terrorism, war (including the ongoing ~~conflict~~ **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- clinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts, 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, liability, including potential lawsuits from patients, collaborators, employees, stockholders or other third parties **,** and liability under foreign, federal and state laws that protect the privacy and security of personal information, and the development and potential commercialization of our product candidates could be delayed **. 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. The risk of cyber- attacks is increased with employees working remotely. Remote work increases the risk we may be vulnerable to cybersecurity- related events such as phishing attacks and other security threats** . Risks Related to Our Industry Before obtaining regulatory approval for the commercial distribution of our product candidates, 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. 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. We currently have multiple programs in clinical development, including internal and ~~partnered~~ **collaborated** programs in Phase 3 development, as well as several earlier- stage clinical programs. However, we may not be able to further advance any of our product candidates through clinical trials and regulatory approval .If we enter into clinical trials,the 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 ~~APOLLO- B and~~ HELIOS- B Phase 3 clinical ~~trials~~ **trial** of ~~patisiran and~~ vutrisiran ~~,respectively~~ ,which ~~are~~ **is** investigating the potential of ~~patisiran and~~ vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy. ~~We announced positive topline results from the APOLLO- B study in August 2022,and patients enrolled in the study are receiving patisiran as part of an open- label extension period.~~ While ~~both patisiran and~~ vutrisiran ~~have~~ **has** demonstrated positive results in patients with hATTR amyloidosis with polyneuropathy,we cannot be certain that the results from HELIOS- B will be positive or that the results from ~~APOLLO- B and / or~~ HELIOS- B will support approval of ~~patisiran and / or~~ 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 ~~patisiran~~ **vutrisiran,could have a material adverse effect on our business,prospects,operating results and financial condition.Moreover,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** . Additionally, several of our planned and ongoing clinical trials utilize an " open- label " trial design. An " open- label " clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or 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~~ **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 ~~for which we include an open- label clinical trial~~ when studied in a **blinded,** controlled environment with a placebo or active control . If we enter into clinical trials..... clinical trials and proven safe and effective . In addition, we, the FDA or other applicable regulatory authorities, or an **institutional review board, or** IRB, or similar foreign review board or committee, may delay initiation of or suspend clinical trials of a product candidate at any time for various reasons, 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, adverse side effects of a product candidate or related product on healthy volunteer subjects or patients in a clinical trial could result in our decision, or a decision by the FDA or foreign regulatory ~~authorities~~ **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 ~~. For example, in October 2016, we announced our decision to discontinue development of revusiran, an investigational RNAi therapeutic that was being developed for the treatment of patients with cardiomyopathy due to hATTR amyloidosis. Our decision followed the recommendation of the revusiran ENDEAVOUR Phase 3 study Data Monitoring Committee to suspend dosing and the observation of an imbalance in mortality in revusiran- treated patients as compared to those on placebo~~ . 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** ~~For~~ - **or** ~~example, we or~~ **our collaborators** ~~our partners~~ may experience difficulty enrolling our clinical trials ~~, including, but not limited to, the ongoing clinical trials for fitusiran,~~ due to the availability of existing approved treatments, as well as other investigational treatments in development. ~~In addition~~ **For example** , in November 2018 we announced that due to recruitment challenges, we had discontinued a Phase 2 study of cemdisiran in atypical hemolytic uremic syndrome and ~~are~~ **were** focusing our cemdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment, ~~including the enrollment delays in our KARDIA- 1 Phase 2 monotherapy study of~~

~~zilebesiran resulting from the ongoing situation in Ukraine,~~ 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 ~~such as the COVID- 19 pandemic~~ , can result in increased costs, longer development times or termination of a clinical trial. Although our ~~investigational~~ 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 ~~with hemophilia A without inhibitors~~ 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 ~~. In~~ **and, in** October 2021, Sanofi announced that a potential filing date for fitusiran ~~has~~ **had** been moved to 2024 due to the introduction of a revised dosing regimen in the ongoing phase 3 studies. **In addition** ~~As demonstrated by the discontinuation of our revusiran program in October 2016~~ , the ~~temporary suspension of dosing in September 2017 in our fitusiran studies, as well as Sanofi' s voluntary pause of fitusiran studies in October 2020, the occurrence of SAEs and / or AEs can result in the suspension or termination of clinical trials of a product candidate by us, our partners, or the FDA or a foreign regulatory authority. 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., ~~an~~ independent ethics ~~committee~~ **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 ~~investigation~~ **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 ~~we develop~~ 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 ~~we~~ **our product candidates** experience any such problems, we may not have the financial resources **necessary** to continue development of the **affected** product candidate ~~that is affected,~~ or ~~development of~~ any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate ~~and for~~ **or any of our** other product candidates ~~we are developing~~ . 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 ~~we expect~~ **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 the ongoing conflict in Ukraine; • disruptions caused by man- made or natural disasters or **pandemics, epidemics or** public health **emergencies** ~~pandemics or epidemics~~ or other business interruptions ~~, including the ongoing COVID- 19 pandemic~~ ; • 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 ~~the~~ 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 ~~by~~ individuals using drugs similar to our **products or** product candidates; • poor or disappointing effectiveness of our product candidates during clinical trials; • 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 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 • interpretations of data by the FDA and similar foreign regulatory agencies that differ from ours. Even if we successfully complete clinical trials of our product candidates, any given product candidate may not prove to be a safe and effective treatment for the disease for which it was being tested. We or our ~~partners~~ **collaborators** may be unable to obtain U. S. or foreign regulatory approval for our or our ~~partnered~~ **collaborated** product candidates and, as a result, we or our ~~partners~~ **collaborators** may be unable to commercialize such product candidates. Our and our ~~partnered~~ **collaborated** product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling,

storage, pricing, marketing and distribution of drugs. Rigorous nonclinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the U. S. and 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 ~~partners~~ **collaborators** are developing will not obtain the regulatory approvals necessary for us or our collaborators to begin selling them, or, in the case of ~~patisiran and~~ vutrisiran, will not obtain regulatory approval to be sold for **a** broader ~~indications~~ **indication** than ~~are~~ **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 ~~, including patisiran, while positive,~~ is not sufficient to support the approval of an application for regulatory approval. ~~In February~~ **For example, although we reported positive results from the APOLLO- B Phase 3 study 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 ~~accepted~~ **issued a CRL in response to** our sNDA for **patisiran** ~~ONPATTRO for filing and set an action date of October 8~~ , **indicating** ~~2023, under the PDUFA. The FDA also indicated in~~ the sNDA **could** ~~filing communication letter that it is planning to hold an advisory committee meeting to discuss the application and that it had~~ not ~~identified any potential review issues at such time. Even though the sNDA has been accepted for filing, we may receive a complete response letter rather than approval, including for reasons that may~~ be **approved in its present form** ~~identified during a meeting of the advisory committee~~ . 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** ~~predictably~~ **predictable** or ~~uniformly~~ **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 ~~partners~~ **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 ~~drugs~~ **product candidates** we ~~or our~~ **or** ~~partners~~ **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 ~~partners~~ **collaborators** may submit. Moreover, the FDA may respond to these submissions by defining requirements we or our ~~partners~~ **collaborators** may not have anticipated. Such responses could lead to significant delays and increased costs in the development of our or our ~~partnered~~ **collaborated** product candidates. In addition, because there may be approved treatments for some of the diseases for which we or our ~~partners~~ **collaborators** may seek approval, including ~~patisiran and~~ vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy, or treatments in development which are approved by the time we or ~~they apply~~ **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 ~~, if any,~~ are not only safe and effective, but safer **and /** or more effective than existing **approved** products. Interruption or delays in the operations of the FDA, EMA and comparable foreign regulatory agencies ~~due to the COVID- 19 pandemic,~~ may impact the review, inspection and approval timelines for our or our ~~partnered~~ **collaborated** product candidates. During the COVID- 19 public health emergency, the FDA ~~has~~ worked to ensure timely reviews of applications for medical products in line with its user fee performance goals and ~~conduct~~ **conducted** mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. ~~However~~ **In addition** , ~~the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre- approval inspection or an inspection of clinical sites is required and due to the ongoing COVID- 19 pandemic and travel restrictions the FDA is unable to complete such required inspections~~ during ~~the review period. 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** ~~complete response letter~~ 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 (~~which is~~ the trade name under which inclisiran is marketed in the U. S.) in December 2021. ~~The~~ **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 ~~agency~~ **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 ~~results~~ **condition** . For instance, the FDA may request additional clinical or other data or information in connection with the regulatory review of our or our ~~partners~~ **collaborators** ' product candidates ~~, including patisiran~~ , including by issuing a complete response letter which may require that we or our **collaborators** ~~partners'~~ submit additional clinical or other data or impose other conditions that must be met in order to secure final approval of our or our ~~partners~~ **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. Any delay or failure in obtaining required approvals for our product candidates or our ~~partnered~~ **collaborated** product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we or our ~~partners~~ **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 negatively impacted . Furthermore, any regulatory approval to market any product ~~, including patisiran,~~ may be subject to limitations on the approved uses for which we or our ~~partners~~ **collaborators** may market the product or the labeling or other restrictions, which could limit each such product' s market opportunity and have a negative impact on our **business, prospects, operating** results ~~of operations~~ **and financial condition** and our stock price. 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 ~~partners~~ **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 ~~the~~ **our** ~~product~~ **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 ~~authorities~~ **authority** outside the U. S. and vice versa. Even if we or our ~~partners~~ **collaborators** obtain regulatory approvals, our marketed ~~drugs~~ **products** will be subject to ongoing regulatory oversight. If we or our ~~partners~~ **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 any initial regulatory approval of ~~drugs~~ **a product** we ~~or our~~ **or** ~~partners~~ **our collaborators** may develop, including our four approved ~~drugs~~ **products** , we will ~~also~~ be subject to continuing regulatory oversight, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This ~~would include~~ **includes** results from any post- marketing tests or surveillance to monitor the safety and efficacy of our approved ~~drugs~~ **products** or other ~~drug~~ products required as a condition of approval or **otherwise** agreed to by us. The regulatory approvals that we receive for ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO, as well as any regulatory approvals we receive for any ~~other~~ **of our** product candidates may also be subject to limitations on the approved uses for which the product may be marketed, including any expanded label for ~~ONPATTRO or~~ AMVUTTRA. Other ongoing regulatory requirements include, among other things, submissions of safety and other post- 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 that we conduct post- approval. In addition, we are conducting, and intend to continue to conduct, clinical 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 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 ~~drug~~ **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 ~~drug~~ **product** . As our approved products are used commercially, we or others could identify previously unknown side effects or known side effects could 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** ~~more modest~~ 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 or clinical studies, 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 ~~prevent~~ **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 ~~facilities or our~~ **or our** ~~CMOs~~ **CMO' s** ~~, or our or their~~ manufacturing processes or facilities, may result in restrictions on the drug or CMO or facility, including delay in approval or, in the future, withdrawal of the ~~drug~~ **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, 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 addition,~~ in 2020 ~~, we~~ completed construction of a cGMP manufacturing facility for drug substance for clinical and, eventually, commercial use ~~. We~~ **, 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 foreign jurisdictions in which we ~~may~~ seek to market our products, we or they may be subject to,

among other things, fines, warning 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, injunction, civil penalties and criminal prosecution ~~. We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities or promoting our commercially approved products in a way that violates applicable regulations~~ . Physicians have the discretion to prescribe approved drug products for uses that are not described in the product' s labeling and that differ from those approved by the FDA or other applicable regulatory agencies. Off- label uses are common across medical specialties. Although the FDA and other regulatory agencies that approve drug products do not regulate a physician' s practice of medicine or choice of treatments, the FDA and other regulatory agencies regulate a manufacturer' s communications regarding off- label use and prohibit off- label promotion, as well as the dissemination of false or misleading labeling or promotional materials, including by their agents. Manufacturers and their agents may not promote drugs for off- label uses or provide ~~off- label~~ information in the promotion of drug products that is not consistent with the approved labeling for those products. For example, we may not **currently** promote ONPATTRO or AMVUTTRA in the U. S. for use in any indications other than the treatment of ~~the polyneuropathy 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 ~~. In April 2021~~ , ~~we received a subpoena from the U. S. Department of Justice, U. S. Attorney' s Office for the District of Massachusetts, requiring production of documents pertaining to our marketing~~ and **if** ~~promotion of ONPATTRO (patisiran)~~ in ~~the U. S. We are cooperating with the U. S. Attorney' s Office and producing documents in response to the subpoena. Current and former officers and employees also have received subpoenas in connection with the preservation and production of related materials. Given the ongoing nature of the investigation, it is possible that the U. S. Attorney' s Office for the District of Massachusetts or other~~ -- **the future** ~~government entities may request other information from, or issue other subpoenas, findings or similar documents to, us, our related entities and their respective directors, officers and employees. If~~ we are found to have improperly marketed or promoted **any of our commercial products** ~~ONPATTRO in connection with such subpoenas~~ , we may be subject to a broad range of civil, administrative and criminal penalties, including injunctive relief related to ~~ONPATTRO~~ **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 ~~, financial condition~~ or divert financial and management resources from our core business, and would have a material adverse effect on our business, **prospects, operating results or** financial condition ~~and results of operations~~ . 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 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 ~~above~~ **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 ~~prevent us from becoming profitable~~ **adversely affect our business, prospects, operating results and financial condition** . The product candidates that we are developing are based upon new technologies or 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 ~~product~~ **products** , or to provide favorable reimbursement. Other factors ~~that~~ we believe will materially affect market acceptance of our ~~product~~ **products** ~~candidates~~ 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, ~~one of our two commercially approved therapeutics for the treatment of the polyneuropathy of hATTR amyloidosis in adults,~~ ONPATTRO ~~,~~ utilizes an intravenous mode of administration with pre- medication that physicians and / or patients may not

readily adopt, ~~or~~ **and** which may not compete favorably with other available options **for the treatment of hATTR amyloidosis with polyneuropathy in adults** , including inotersen, marketed by Ionis in several countries, which is administered subcutaneously, or tafamidis, marketed by Pfizer in several countries, 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. ~~Patisiran~~ **Assuming positive results from the HELIOS- B Phase 3 clinical trial, vutrisiran** , if approved for the treatment of ATTR amyloidosis with cardiomyopathy, 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** ~~Even if~~ we ~~successfully~~ **are not able to continue to develop and** scale **these** ~~our commercial~~ capabilities, **we** ~~the market~~ may not be ~~receptive~~ **able** to ~~our~~ **successfully** ~~commercial~~ **commercialize our current and any future** products. ~~Having~~ **We** received our first product approval in August 2018 **and** ~~, we~~ have established ~~our~~ 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** ~~several of our late- stage~~ 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 ~~where~~ **with respect to which** we ~~may~~ retain ~~certain product~~ 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** , 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 ~~cannot~~ **fail to** raise awareness of these diseases and diagnosis is not improved, our ~~revenue~~ **business, prospects, operating results** and **financial condition** ~~ability to achieve profitability from these products~~ may be adversely affected. Our estimates regarding the potential market size for ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or any future products at the time we commence commercialization, 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 ~~of operations~~ and financial condition ~~. For example, the initial indication approved by the FDA for ONPATTRO is for the treatment of the polyneuropathy of hATTR amyloidosis and not for the treatment of cardiomyopathy or other manifestations of the disease. In addition, the U. S. label does not include cardiac data included in our APOLLO- B Phase 3 study results. This had an adverse impact on the market opportunity for ONPATTRO in the U. S. While data from the APOLLO- B study of patisiran in ATTR amyloidosis patients with cardiomyopathy was positive, the FDA may determine that the data is not supportive of a label expansion of ONPATTRO for the treatment of cardiomyopathy, which would further impact ONPATTRO' s market opportunity~~ . In addition, our efforts to raise disease awareness and improve diagnosis of our relevant disease states **were** ~~have been and may in the future be~~ 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 ~~cannot~~ **are unable to** successfully 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 ~~other programs~~ **product candidates** move through late stages of development. However, a number of our ~~programs~~ **product candidates** are currently in the earlier stages of development, and we will not be able to assess the impact of ~~price~~ **such** regulations ~~for~~ **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., pharmaceutical pricing is subject to both government and public scrutiny and calls for reform, and the U. S. government has continued to focus 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 of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient 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 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 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 newly designed Part D benefit structure compared to the pre- IRA benefit design. Under the IRA' s Price Negotiation Program, a 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 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 and may have 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 administration has indicated that lowering prescription drug prices is a priority, but we do not know the impact of policies established by the Biden administration to lower the prices of prescription drug prices. For example, the Center for Medicare and Medicaid Innovation is developing new models intended to lower drug costs under Medicare and Medicaid, including designing new payment methods for 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 proposed measures may require authorization through additional legislation to become effective, and the current U. S. presidential administration may reverse or otherwise change 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, product access, 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 of drugs from Canada and the Most Favored Nation, or MFN, Model may materially and adversely affect the price we receive for any of our 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, and we expect ongoing initiatives in the U. S. to increase pressure on drug pricing. Such reforms could have a material and adverse effect on our anticipated revenues from 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~~ **ONPATTRO,AMVUTTRA,GIVLAARI** ~~an~~ **and** ~~appropriate return on~~ **OXLUMO.Under currently applicable U.S.law,certain drugs that are not usually self- administered (including injectable drugs) may be eligible for coverage under the Medicare Part B program if:• they are incident to a physician' s services;• they are reasonable and necessary for the diagnosis** ~~our~~ **or** ~~investment in product development~~ **treatment of the illness or injury for which they are administered according to accepted standards of medical practice;and • they have been approved by the FDA and meet other requirements of the statute** .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~~ **drug** .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 **payments allowed for** 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 **Medicare** 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~~ . 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 ~~payers~~ **payors** on these agreements is also intended to provide more ~~certainty to~~ **confidence regarding** ~~them~~ **the** ~~for their investment~~ **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 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 ~~6~~ **3** . 4 % 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. ~~Some~~ **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** ~~the~~ **them** ~~drugs we market need to be administered under the supervision of a physician or other healthcare professional on an outpatient basis~~ , including **patient assistance** ONPATTRO, AMVUTTRA, GIVLAARI and OXLUMO..... 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. President Biden signed an~~ **and** ~~Executive Order on July 9, 2021 affirming the administration' s policy to (i) support legislative reforms that would lower the prices of prescription drugs, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower- cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs the U. S. Department of Health and Human Services, or HHS, to provide a report on actions to combat excessive pricing of prescription drugs, continue to clarify and improve the approval framework for generic drugs and identify and address any efforts to impede generic drug competition, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA' s implementing regulations. The FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. In response, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the Most Favored Nation, or MFN, Model may materially and adversely affect the price we receive for any of our commercially approved products. Further, on November 20, 2020, CMS issued an Interim Final Rule implementing the MFN Model under which Medicare Part B reimbursement rates will be calculated for certain drugs based on the lowest price drug manufacturers receive in OECD countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U. S. states and territories for a seven- year period beginning January 1, 2021, and ending December 31, 2027. However, on December 29, 2021, CMS rescinded the proposed MFN rule. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point- of- sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors have been delayed until January 1, 2023, requiring manufacturers to ensure the full value of~~ co- pay ~~assistance~~ **coupon programs for eligible patients. It** is **possible** ~~passed on to the patient or these dollars will count toward the Average Manufacturer Price and Best Price calculation of the drug. On May 17, 2022, the U. S. District Court for the District of Columbia granted the Pharmaceutical Research and Manufacturers of America' s motion for summary judgement invalidating the accumulator adjustment rule. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the current U. S. presidential administration may reverse or otherwise change these measures, both the current U. S. presidential administration and Congress have indicated~~ that **changes in insurer policies regarding co** ~~they will continue to seek new legislative measures to control drug costs. 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. Specifically, there have been several recent U. S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. A number of other legislative and regulatory changes in the healthcare system in the U. S. and other major healthcare markets have been proposed or enacted in recent months and years, and such efforts have expanded substantially in recent years. These developments could, directly or indirectly, affect our ability to sell ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO or future products, if approved, at a favorable price. In particular, in March 2010, the ACA was signed into law. This legislation changed the system of healthcare insurance and benefits intended~~

~~to broaden coverage and control costs. The law also contains provisions that affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Among the provisions affecting pharmaceutical companies are the following: • Mandatory rebates for drugs sold into the Medicaid program were increased, and the rebate requirement was extended to drugs used in risk- based Medicaid managed care plans. • The 340B Drug Pricing Program under the Public Health Service Act was extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities. • Pharmaceutical companies are required to offer discounts on brand- name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the " donut hole. " • Pharmaceutical companies are required to~~ pay **coupons (** ~~an annual non- tax deductible fee to the federal government based on each company' s market share of prior year total sales of branded products to certain federal healthcare programs,~~ such as **co** ~~Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal healthcare program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition. • The law provides that approval of an application for a follow- on biologic product may not become effective until 12 years after~~ **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** ~~the~~ **these** ~~date on co-~~ **pay coupon programs and patient support programs,** which **could result in fewer patients using affected** ~~the reference innovator biologic product was first licensed by the FDA, with a possible six- month extension for pediatric~~ products ~~. After this exclusivity ends~~ , ~~it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability. • The law creates a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected. • The law expands eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133 % of the federal poverty level, thereby potentially increasing a manufacturer' s Medicaid rebate liability. • The law expands the entities eligible for discounts under the Public Health Service Act pharmaceutical pricing program. • The law expands healthcare fraud and abuse laws, including the civil FCA and the federal Anti- Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance. • The law establishes new requirements to report financial arrangements with physicians and teaching hospitals and to annually report drug samples that manufacturers and distributors provide to physicians. • The law establishes a new Patient- Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. • The law established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery methods. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $ 1. 2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation' s automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of 2 % per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID- 19 pandemic. Following the suspension, a 1 % payment reduction began 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. 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. Further, there have been several changes to the 340B Drug Pricing Program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain healthcare facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B Drug Pricing Program, and CMS subsequently altered the fiscal years 2019 and 2018 reimbursement formula on specified covered outpatient drugs. The court ruled this change was not an~~ **and therefore** ~~" adjustment " which was within the Secretary' s discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U. S. Court of Appeals for the District of Columbia Circuit overturned the district court' s decision and found that the changes were within the Secretary' s authority. On September 14, 2020, the plaintiffs- appellees filed a Petition for Rehearing En Banc (i. e., before the full court), and the court denied this petition on October 16, 2020. Plaintiffs- appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On July 2, 2021, the Supreme Court granted the petition. On June 15, 2022, the Supreme Court unanimously reversed the Court of Appeals' decision, holding that HHS' s 2018 and 2019 reimbursement rates for 340B hospitals were contrary to the statute and unlawful. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any. The IRA, which among other things, allows for CMS to negotiate prices for certain single- source drugs and biologics reimbursed under Medicare Part B and Part D, beginning with ten high- cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. The legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated " maximum fair price " under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. Further, the legislation caps Medicare beneficiaries' annual out- of- pocket drug expenses at $ 2, 000. Under the IRA, a second FDA approval for vutrisiran for Stargardt Disease would cause us to~~

~~lose the single- 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 in Stargardt Disease. The effect of the IRA on our business and the healthcare industry in general is developing and may have an additional adverse impact on our industry. The full effects of the U. S. healthcare reform legislation cannot be known until the law is fully implemented through regulations or guidance issued by CMS and other federal and state healthcare agencies. The financial impact of the U. S. healthcare reform legislation over the next few years will depend on a number of factors, including, but not limited, to the policies reflected in implementing regulations and guidance, and changes in sales volumes for products affected by the new system of rebates, discounts and fees. This legislation may also have a positive impact on our future net sales, if any, by increasing the aggregate number of persons with healthcare coverage in the U. S. Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. On June 17, 2021, the U. S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court' s decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for the purpose of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business. At the state level, legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing. Some of these measures include price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. 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. Further federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the U. S. to increase pressure on drug pricing. Such reforms~~ could have ~~an~~ **a material** adverse effect on ~~anticipated revenues from one or~~ **our sales, business,** ~~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 overall~~ financial condition ~~and ability to develop drug candidates~~. 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 ~~FCPA~~ **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** ~~state and national~~ anti- bribery and anti- money laundering laws ~~in the countries in which we conduct activities~~. Anti- corruption laws are interpreted broadly and prohibit companies and their **officers, directors,** employees, agents, contractors, and other ~~collaborators~~ **third- party representatives** from **directly or indirectly** authorizing, promising, offering, ~~or~~ providing, **soliciting** ~~directly or indirectly~~, ~~improper~~ **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 ~~our employees,~~ agents, contractors, and ~~other collaborators~~ **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 ~~civil and criminal~~ fines and penalties ~~, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation~~, reputational harm, and other **adverse** consequences. We remain focused on these laws and the activities they regulate and, as detailed ~~above~~ **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 ~~is~~ **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** ~~there~~ **other stakeholders** can ~~be~~ **put** considerable pressure ~~by governments and other stakeholders~~ 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 ~~. In some countries, we may be required to conduct a clinical study or other studies that compare the cost- effectiveness of a product candidate to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time- consuming and costly~~ . We cannot be sure that such prices and reimbursement will be acceptable to us or our **collaborators** ~~strategic partners~~ . 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** ~~strategic partners~~ and the potential profitability of our approved products or any future products in those countries would be negatively affected. ~~Another~~ **We could also suffer** impact from ~~the~~ tightening pricing ~~control~~ **controls on account of** ~~could be felt from~~ greater competition from less expensive generic or biosimilar products once **patent or** ~~the~~ **other** exclusivity expires ~~; the~~ **. Certain** governments have adopted policies to switch prescribed products to generic versions ~~in order~~ to **reduce** ~~cut the medical cost~~ **costs** . 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 ~~affect~~ **negatively impact** our ability to develop, market and sell our products and may harm our reputation. **Healthcare providers** ~~As a manufacturer of pharmaceuticals~~ , **physicians** ~~we are subject to federal~~ , ~~state,~~ and ~~comparable foreign~~ **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 ~~pertaining to fraud~~ **that may constrain our business or financial arrangements** and ~~abuse and patients' rights~~ **relationships through which we market** , **sell** ~~in addition to legal obligations related to privacy~~ , ~~data protection~~ and ~~information security~~ **distribute our products** . ~~These~~ **Restrictions under applicable federal and state healthcare** laws and regulations include **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 for, the purchase, lease, order, arrangement, or recommendation of any 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 ~~for each violation, plus up to three times the remuneration involved~~ , 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 prohibit, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment 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 impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or **Medicaid** ~~state healthcare program~~ 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** ~~a state healthcare program~~ , unless an exception applies. • The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created **, among other provisions,** federal criminal statutes that prohibit 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 in connection with the delivery of, or payment for, healthcare benefits, items or services ~~relating to healthcare matters~~ . 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 ~~imposes~~ **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 ~~ACA~~ **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 physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non- physician providers such as physician assistants and nurse practitioners, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit ~~required~~ **timely, accurate and complete** information may result in civil monetary penalties ~~for all payments, transfers of value or ownership or investment interests that are not timely, accurately, and completely reported~~

~~in an annual submission~~ . • Federal price reporting laws, which require manufacturers to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and / or discounts on approved products. • Federal statutory and regulatory requirements applicable to pricing and sales of ~~product~~ **products** to ~~Federal~~ **federal** ~~Government~~ **government** ~~Agencies~~ **agencies** . • Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers. • 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, 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 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 ~~. Failure to comply with our obligations under the privacy regime could expose us to significant fines and / or adverse publicity, which could have material adverse effects on our reputation and business~~ . • The California Consumer Privacy Act of 2018, **as amended by the California Privacy Rights Act of 2020,** or **, collectively, the** CCPA, ~~effective as of January 1, 2020,~~ that **, among other provisions,** gives California residents ~~expanded~~ rights ~~to~~ **of** access **, correction, portability,** and ~~require~~ deletion of their personal information ~~,~~ **and various** opt out ~~of certain personal information sharing~~ **rights. The CCPA also imposes various obligations on regulated businesses** , **such as to maintain privacy notices, implement reasonable security practices,** and ~~receive detailed information about how their personal information~~ **include specific terms in contracts with data processors. The CCPA also created a new state agency that** is ~~used~~ **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 have been enacted in more** ~~that~~ **than** ~~is expected to increase~~ **ten other states and proposed in several others. Three states have additionally enacted laws regulating " consumer health** data ~~breach litigation. • Additionally~~ , **" which** ~~a new California ballot initiative, the California Privacy Rights Act of 2020, or CPRA, was passed in November 2020. Effective as of January 1, 2023, the CPRA imposes~~ **impose** additional obligations on **regulated entities beyond state comprehensive privacy laws** ~~companies covered by the legislation and will significantly modify the CCPA~~ , ~~including by expanding~~ **such as to obtain distinct consents for certain collection and sharing of** ~~consumers~~ **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** ~~rights~~ **right of action** ~~with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. Furthermore, similar laws were enacted in four other states and proposed in numerous others~~ . The effects of the CCPA and ~~the~~ **other** ~~CPRA~~ **state privacy laws** are 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 require pharmaceutical manufacturers to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring manufacturers to report information related to payments to physicians and other healthcare ~~provides~~ **providers** or marketing expenditures and 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** compliance efforts. 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, ~~loss of eligibility to obtain approvals from the FDA,~~ 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 Health and Human Services, **or the OIG,** any of which could **materially and** adversely affect our **business, prospects, operating results or** financial ~~results~~ **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 ~~other~~ 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 ~~: • adverse regulatory inspection findings; • untitled letters or warning letters; • voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals; • restrictions on~~ , ~~or prohibitions against, marketing our products; • restrictions on, or prohibitions against, importation or exportation of our products; •~~

~~suspension of review or refusal to approve pending applications or supplements to approved applications; • exclusion from participation in government- funded healthcare programs; • exclusion from eligibility for the award of government contracts for our products; • suspension or withdrawal of product approvals; • product seizures; • injunctions; and •~~ civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment. Moreover, federal, state ~~or~~ **and** foreign laws or regulations are subject to change, and while we, our collaborators, CMOs and / or service providers currently may be compliant, ~~that~~ **we** could ~~change~~ **fall out of compliance** due to changes in interpretation, prevailing industry standards or the legal structure. 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, 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 ~~some~~ 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** ~~out of~~ government claims challenging the legality of ~~their~~ patient assistance programs under a variety of federal and state laws. **We have made and** ~~It is possible that we~~ 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 ~~choose to~~ do so, and if we or our ~~vendors or~~ donation recipients are deemed to ~~fail to comply with~~ **be acting in violation of** relevant laws, regulations or evolving government guidance ~~in the operation of these programs~~, we could be subject to damages, fines, penalties, or other criminal, civil, or administrative sanctions or enforcement actions. We ~~cannot ensure that our compliance controls, policies, and procedures will be sufficient to protect against acts of our employees, business partners, or vendors that may violate the laws or regulations of the jurisdictions in which we operate. Regardless of whether we have complied with the law, a government investigation could impact our business practices, harm our reputation, divert the attention of management, increase our expenses, and reduce the availability of foundation support for our patients who need assistance. We~~ are subject to governmental regulation and other legal obligations ~~, particularly~~ 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** ~~put in place~~ 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 ~~to~~ 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 ~~organisational~~ **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 ~~to legitimize~~ **as a basis for lawful transfer of personal** data ~~transfers~~ 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~~ **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 ~~also~~ 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 ~~position~~ **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 ~~to have reached~~ a political agreement on a new " Trans- Atlantic Data Privacy Framework " **to** ~~, which will~~ replace the invalidated Privacy Shield ~~and on December 13~~ **. The framework introduced new binding safeguards to address the concerns raised by the CJEU in Schrems II. On July 10** , ~~2022~~ **2023** , the EC ~~published a draft~~ **announced that it had adopted its** adequacy decision ~~on~~ **for that data privacy framework, labelled** the ~~Trans~~ **EU** - ~~Atlantic~~ **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** ~~so that~~ we do not expect to operate in a uniform legal landscape in the EU. In addition, the UK **Government** has ~~announced plans~~ **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** ~~the country~~ ' s data protection ~~legal framework in its Data Reform~~ **regime following Brexit. If passed, the final version of the UK** Bill **may** ~~, but these~~ have ~~been put on hold~~ **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 ~~where~~ **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 ~~they~~ - **the** ~~are~~ **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 ~~could require~~ **requires** ~~us to~~ **that we** take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, ~~or~~ **and,** in some cases, ~~impact~~ **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** ~~position, results of operations and cash flows~~ . 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 legislation amending the statute, including the Bipartisan Budget Act of 2018, these reductions will stay in effect through 2030 unless additional Congressional action is taken. Pursuant to the ~~CARES~~ **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 ~~full impact~~ **2 % payment reduction resumed** on ~~our business~~ **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** ~~these~~ - **three** ~~automatic cuts~~ **to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for 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 ~~uncertain~~ **prescribed or used** . ~~If other federal~~ **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** ~~reduced, any budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the NIH to continue to function~~ . 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. ~~Further,~~ **If we fail to comply with our obligations under the 340B Drug Pricing Program or** ~~there~~ **other** ~~has been heightened~~ **U. S.** governmental ~~scrutiny recently over the manner in~~ **pricing programs, we could be subject to additional reimbursement requirements, 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~~ **Drug** ~~manufacturers set prices~~ **Pricing Program, Medicaid Drug Rebate Program, and a number of other federal and state government pricing programs in the U. S. in order to obtain coverage** for **our** ~~their marketed~~ products ~~, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed~~ **by certain government health care programs. These programs generally require that we provide discounts or pay rebates** to ~~, among~~ **certain payers when our products are dispensed to beneficiaries of these programs. These programs may also impose** other ~~things~~ **requirements** , ~~bring more transparency~~ **including certain price reporting requirements. Changes** to ~~product~~ **our obligations under these government** pricing ~~, review~~ **programs occur frequently and program requirements are often ambiguous. We may be or become subject to penalties as a result of our failure to comply with obligations under** ~~the~~ **these** ~~relationship between~~ **programs, including if we fail to provide timely and accurate information to the government, to pay the correct rebates, or to offer the correct discounted** pricing ~~and manufacturer patient~~ **. Complying with these** programs ~~,~~ and ~~reform government~~ **future changes to these** ~~program~~ **programs** ~~reimbursement methodologies for drug products~~ **can be 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 ~~. Following the decision to discontinue clinical development of revusiran, we conducted a comprehensive evaluation of available revusiran data. We reported the results of this evaluation in August 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. In addition, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. Notwithstanding the risks undertaken by all persons who participate in clinical trials, and the information on risks provided to study investigators and patients participating in our clinical trials, including the revusiran and fitusiran studies, it is possible that product liability claims will be asserted against us relating to the worsening of a patient' s condition, injury or death alleged to have been caused by one of our product candidates, including revusiran or fitusiran~~ . 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** ~~comply with~~ 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 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~~ **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, information obtained in the course of clinical studies, 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 ~~and~~ **, prospects, operating** results ~~of operations~~ **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 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 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 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 ~~licensees~~ **collaborators** may be required to obtain licenses under third- party patents to market one or more of our or our ~~partner'~~ **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 ~~licensees~~ **collaborators** . If licenses are not available to us or not available on reasonable terms, 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 ~~during certain~~ **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 ~~of the United States~~ 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 ~~, broad patent scope~~ and to maximize patent term restoration or extension on patents covering our **product candidates and** products may lead to loss of exclusivity and ~~early~~ 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 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 ~~to which~~ we ~~are~~ **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 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 ~~inter partes~~ **pre-** and post- grant review proceedings ~~introduced by provisions of the AIA, which became available to third party challengers on September 16, 2012,~~ 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 ~~of~~ **for silencing** ANGPTL3, arguing that the granted claims are invalid. ~~An~~ **Following an** oral hearing ~~was held at the EPO~~ in February 2021, ~~where~~ 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. ~~An oral~~ **Oral** ~~hearing~~ **hearings** ~~is~~ **are** anticipated **in these proceedings** at ~~a time~~ **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 ~~licensees~~ **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 ~~licensees~~ **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 ~~and we are not able to obtain a license on reasonable terms~~ , 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, during 2017 and 2018, Silence **Therapeutics, plc, or Silence,** filed claims in several jurisdictions, including the High Court of England and Wales, and named us and our wholly owned subsidiary Alnylam UK Ltd. as co- defendants. Silence alleged various claims, including that 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 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, in October 2017 Silence sued us in the UK alleging that ONPATTRO and other investigational RNAi therapeutics we or MDCO ~~are~~ **were** developing infringed one or more Silence patents. 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 ~~as well~~ . During the pendency of this litigation, as well as the Dicerna litigation described ~~above~~ **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. 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. ~~We~~ **In April 2018, we** and Dicerna settled **all claims in** the ~~ongoing~~ litigation between us ~~in April 2018~~ . In March 2022, we announced that we separately filed suit in United States District Court for the District of Delaware against Pfizer and Moderna ~~, Inc.,~~ 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 ~~a new~~ **an additional** lawsuit in United States District Court for the District of Delaware against each of Pfizer / BioNTech and Moderna seeking damages for infringing ~~our newly granted~~ U. S. Patent No. 11, 382, 979 **, or the' 979 patent** . The ~~Court~~ **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 and 11, 633, 480 in the more recently filed suits against both Pfizer and Moderna and also 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. Subsequently, 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 did not affect one of the patents in the lawsuit filed against Moderna on May 26, 2023, and that case is going forward on a schedule with an anticipated trial date in the latter half of 2025. In September 2023, we and Pfizer / BioNTech agreed to consolidate the 2022 Lawsuit and 2023 lawsuits into one case, which will require moving the trial date 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 ~~ongoing~~ 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, ~~if~~ **or** at all. In addition, such licenses are ~~likely to be~~ **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 profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our collaborations 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 ~~any other~~ product candidates ~~that we develop, or we could lose certain rights to grant sublicenses~~ . 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 our second amended and restated strategic collaboration and license agreement as a result of the January 2018 ~~amendment~~ **restructuring** of our collaboration agreement with Sanofi and the related Exclusive TTR License and AT3 License Terms. 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 of 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. 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 ~~rejecting~~ **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, 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, ~~others~~ - **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 ~~competitive~~ business ~~position~~ **, prospects, operating results and financial condition** . The pharmaceutical market is intensely competitive ~~. If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to commercialize successfully any drugs that we develop. 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: • ~~much~~ **substantially** greater financial, technical and human resources than we have ~~at every stage of the discovery, development, manufacture and commercialization of products~~ ; • more extensive experience in pre- clinical 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 develop drugs. **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. 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, ~~if~~ **assuming positive results in our HELIOS- B Phase 3 clinical and regulatory** ~~approved~~ **approval** ~~by the FDA~~ , ~~patisiran~~ **vutrisiran** , our RNAi therapeutic in development for **treatment of** ATTR amyloidosis ~~patients~~ with cardiomyopathy, would compete with **VYNDAQEL / VYNDAMAX (** tafamidis **)** , marketed by Pfizer, which is currently approved to treat this disease. ~~We also expect to face competition from new drugs that enter the market. There are a number of drugs currently under development, which may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop and commercialize. For example, we developed ONPATTRO for the treatment of hATTR amyloidosis.~~ In ~~August 2018, the FDA approved ONPATTRO lipid complex injection for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and the EC granted marketing authorization for ONPATTRO for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. We are aware of other approved products used to treat this disease, including tafamidis, and inotersen, developed and marketed by Ionis, as well as product candidates in various stages of clinical development, including eplontersen, an additional~~ -- **addition** ~~investigational drug developed by Ionis in partnership with AstraZeneca~~ , ~~which met co- primary and secondary endpoints in an interim analysis of a Phase 3 study for the polyneuropathy of hATTR amyloidosis, and is currently under regulatory review by the FDA. Finally, we are aware that~~ BridgeBio ~~Pharma, Inc. (formerly Eidos Therapeutics, Inc.), or BridgeBio,~~ announced ~~topline~~ **positive** results from ~~Part A of~~ 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. 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 product candidates in earlier stages of development for the treatment of ATTR amyloidosis with cardiomyopathy, including NTLA** - ~~CM in December 2021~~ **2001** ~~,~~ which ~~did not meet the primary endpoint of the study at month 12. BridgeBio initiated enrollment in Part B of its~~ - **is being developed by Intellia Therapeutics, Inc. and Regeneron and is in** Phase 3 clinical ~~trial of acoramidis~~ **development; NNC-6019 which is being developed by Novo Nordisk and is** in **Phase 3 clinical development; and NI006 which is being developed by Neurimmune AG and AstraZeneca plc and is in Phase 1 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** ~~- PN patients in the fourth quarter of 2020, and anticipates topline results in mid-2023~~ . ~~While we believe that~~ ONPATTRO ~~has~~ and **AMVUTTRA are approved in certain jurisdictions** ~~will continue to have a competitive product profile~~ for the treatment of **certain** patients with hATTR amyloidosis with polyneuropathy **. We are aware of other approved products used to treat this disease** , **including VYNDAQEL / VYNDAMAX (tafamidis),** and **TEGSEDI (inotersen), which is developed and marketed by Ionis. In addition, in December 2023, the FDA approved WAINUA (eplontersen), a drug developed by Ionis in partnership with AstraZeneca plc, for the treatment of hATTR amyloidosis patients with polyneuropathy. There are also product candidates in various stages of clinical development for the treatment of hATTR amyloidosis patients with polyneuropathy. While we believe** that **ONPATTRO and** AMVUTTRA ~~has~~ **have and will continue to have** a competitive product profile ~~in this indication~~ **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. ~~Moreover, positive or negative data and / or the commercial success or failure of competitive products could negatively impact our stock price. For example, our stock price was negatively impacted by the results of Part A of BridgeBio' s Phase 3 clinical trial.~~ If we **or our collaborators** continue to successfully develop product candidates, and obtain approval 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. We are aware of product candidates in various stages of clinical development for the treatment of PH1 which would compete with OXLUMO, our RNAi therapeutic approved in the U. S. and EU for the treatment of this disease, including ~~Oxabact ®~~ **Novo Nordisk' s product RIVFLOZA (nedosiran)** , **which was approved for the treatment of PH1 in September 2023 and is expected to launch in 2024. RIVFLOZA is** a ~~bacteria~~ **once** - ~~based investigational~~ **monthly subcutaneous RNAi** therapy ~~in~~ **that was** ~~development~~ - **developed** ~~by OxThera AB, reloxaliase an investigational enzyme therapy in Phase 3 development for primary or severe secondary hyperoxaluria by Allena Pharmaceuticals, Inc., and nedosiran, an investigational RNAi therapeutic in development~~ by Dicerna ~~for the treatment of primary hyperoxaluria. In July 2019, the FDA granted a Breakthrough Therapy Designation to nedosiran for the treatment of patients with primary hyperoxaluria, and in August 2021, Dicerna reported positive topline results from its PHYOX2 pivotal clinical trial of nedosiran for the treatment of primary hyperoxaluria. Based on the results of the trial, Novo Nordisk submitted an NDA to the FDA in September 2022 for the treatment of PH1 in patients aged six years and older~~ . 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 ~~product candidate~~ **. In addition, several companies have investigational drugs in clinical development for the treatment of PH1, including BridgeBio, Chinook Therapeutics, Inc., and BioMarin Pharmaceutical, Inc** . 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** ~~strategic alliances~~ 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 ~~the~~ **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 ~~drugs~~ **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 ~~not with synthetic siRNAs but~~ 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, ~~Takeda, Marina,~~ Arrowhead ~~, Quark, Silence, Arbutus, Sylentis, Dicerna~~ and its collaborators, ~~WAVE~~ **Takeda Pharmaceutical Company Ltd.** , ~~Areturus~~ **Janssen Pharmaceutics** , **Inc., GlaxoSmithKline plc,** and ~~Genevant~~ **Amgen Inc.; Quark Pharmaceuticals, Inc.; Roche;** ~~Sciences~~ -- **Silence Therapeutics plc and its collaborators** , ~~launched by~~ **AstraZeneca plc, Jiangsu Hansoh Pharmaceuticals Group Co., Ltd., and Mallinckrodt plc;** Arbutus **; Sylentis;** and ~~Roivant Sciences~~ **Novo Nordisk and its collaborators, Boehringer Ingelheim and Eli Lilly and Company** . In addition, we granted licenses or options for licenses to Ionis, Benitec **Biopharma Ltd.** , Arrowhead, Arbutus, Quark, Sylentis and ~~others~~ **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 ~~us~~ **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. ~~Like~~ **Similar to** RNAi therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Akcea ~~(acquired by~~ **Therapeutics, Inc., a wholly owned subsidiary of** Ionis ~~in October 2020)~~ , has received marketing approval for an antisense drug, inotersen ~~that was developed by Ionis,~~ for the treatment of **adult hATTR amyloidosis patients with** stage 1 or stage 2 polyneuropathy ~~in adult patients with hATTR amyloidosis~~ . Several antisense drugs developed by Ionis have been approved and are currently marketed, 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 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~~ **safe** and effective means to deliver siRNAs to the relevant cell and tissue types ~~may be developed by our competitors~~ , ~~and~~ our ability to successfully commercialize a competitive product would be adversely affected. In addition, **third parties are expending** substantial resources ~~are being expended by third parties in the effort~~ to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, **including** both ~~in~~ **private companies and** academic laboratories ~~and in the corporate sector~~ . Some of our competitors have substantially greater resources than we do, and if our competitors ~~are able to~~ negotiate exclusive access to ~~those~~ delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates. ~~The market price of our common stock has fluctuated significantly and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has from time to time experienced extreme price and volume fluctuations, and the biotechnology sector in particular has experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the clinical development progress or operating performance of these companies, including as a result of adverse development events reported by other companies. For example, the trading price for our common stock and the common stock of other biopharmaceutical companies was highly volatile during the initial stages of the COVID- 19 pandemic. These broad market and sector fluctuations have resulted and could in the future result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.~~ Our ~~stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development and commercialization efforts or the development and commercialization efforts of our collaborators and / or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. When the market price of a stock has been volatile as our~~ stock price has been **and may in the future be volatile. From January 1** , ~~holders of~~ **2023 to December 31, 2023, our common stock traded between $ 148. 10 and $ 242. 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 ~~have occasionally brought~~ **in the future could be significantly and adversely affected by many factors, including: • the information contained in our quarterly earnings releases, 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 ~~the company~~ **companies** ~~that issued~~ **following declines in the market price of** ~~the~~ **their securities. This risk is especially relevant for biopharmaceutical companies, which have experienced significant** stock **price volatility in recent years** . For example, ~~on~~ **in** September ~~12,~~ 2019, **we** ~~the Chester County Employees Retirement Fund, individually~~ and **certain** ~~on behalf~~ of ~~all others similarly situated~~ **our current and former directors and officers** , ~~filed~~ **and the underwriters of our November 2017 stock offering were sued in** a **putative** ~~purported securities~~ class action ~~complaint~~ alleging ~~violation~~ **violations** of **the** federal securities laws **. While this matter has been finally settled, we may be the target of additional litigation of this type in the future. Securities litigation** against us ~~, certain of our current and former directors and officers, and the underwriters of our November 14, 2017 public stock offering, in the Supreme Court of the State of New York, New York County. While we believe the allegations in the New York State Securities Litigation were without merit, in August 2021, the parties reached an agreement in principle to resolve the matter. At a hearing on April 12, 2022, the Supreme Court of the State of New York granted final approval to the settlement. Proceedings in the First Department were adjourned until April 2022, pending final approval of any settlement, and were withdrawn as a result of final approval on April 18, 2022. Future litigation~~ 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 ~~such~~ **those** obligations ~~are~~ **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 ~~January~~ **December** 31, 2023, our ~~six~~ **seven** 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 ~~, or we or our officers and directors,~~ 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. ~~Regeneron' s ownership of our common stock could delay or prevent a change in corporate control. As of May 21, 2019, the closing date of the stock purchase in connection with the 2019 Regeneron collaboration, Regeneron held approximately 4 % of our outstanding common stock and has the right to increase its ownership up to 30 %. This concentration of ownership could harm the market price of our common stock in the future by: • delaying, deferring or preventing a change in control of our company; • impeding a merger, consolidation, takeover or other business combination involving our company; or • discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.~~ Anti-takeover provisions in our ~~charter~~ **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** . ~~In addition~~ **Among other things** , these provisions ~~may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include~~ : • **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; • ~~limitations on~~ **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 ~~removal~~ **stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board** of directors; ~~and~~ • **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 of stockholders; • require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to case 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. ~~On September 12~~ **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** ~~2022~~ **2021** ~~, we commenced a private offering~~ **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, we had** $ ~~900~~ **1** . ~~0~~ **02** ~~million~~ **billion** in aggregate principal amount of ~~1 % Convertible Senior~~ Notes **outstanding** ~~due 2027, or the Initial Notes. On September 13, 2022, the initial purchasers in such offering exercised their option to purchase an additional $ 135. 0 million in aggregate principal amount of our 1 % Convertible Senior Notes due 2027, or the Additional Notes, and together with the Initial Notes, collectively referred to as the Notes, bringing the total aggregate principal amount of the Notes to $ 1. 04 billion~~ . The interest rate for the Notes is fixed at 1. 00 % per annum and is payable semi- annually in arrears on May 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, ~~any of~~ **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,** ~~our~~ **or** ~~future~~ **reacting to, changes in our business and our industry; • place us at a disadvantage compared to our competitors who have less** debt ~~agreements may contain restrictive covenants that may prohibit us from adopting~~ **; • limit our ability to borrow additional amounts to fund acquisitions, for working capital and for other general corporate purposes; and • make** ~~any~~ **an acquisition of our company less attractive or more difficult. Any** of these **factors** ~~alternatives. Our failure to comply with these covenants~~ could **harm our business, prospects, operating** ~~result~~ **results** ~~in an~~ **and** ~~event of default which~~ **financial condition. In addition** , if ~~not cured~~ **we incur additional indebtedness, the risks related to** ~~or~~ **our business and our ability to service** ~~waived, could result in the acceleration of our~~ **or** ~~debt~~ **repay our indebtedness would increase** . 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 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, results of operations 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~~ . 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 ~~our~~ **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. ~~Our~~ **The** Notes may become in the future convertible at the option of their holders under certain circumstances. If holders of ~~our~~ **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 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. 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** ~~will be~~ 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** ~~will be~~ treated as a debt discount for accounting purposes, which ~~will be~~ **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, ~~we expect that~~ the shares of common stock underlying the Notes **are** ~~will be~~ reflected in our diluted earnings per share using the " if converted " method, in accordance with ASU 2020- 06. Under ~~that~~ **this** method, diluted earnings per share ~~would~~ **is** generally ~~be~~ 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~~ **Notes** and could materially reduce our reported working capital.