Risk Factors Comparison 2024-02-21 to 2023-02-22 Form: 10-K

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Investing in our securities involves a high degree of risk. You should carefully consider the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. Risks Related to the Commercialization of our Medicines We have limited experience as a company in commercializing medicines and we will have to **continue to** invest significant resources to develop our capabilities. If we are unable to establish effective marketing, sales, market access, distribution, and related functions, or enter into agreements with third parties to commercialize our medicines, we may not be able to generate revenue from our medicines. We currently rely on third parties for the commercialization of our marketed medicines, have limited experience as a company in commercializing medicines and ~~we~~ will have **to continue** to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. There are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. We will also need **to continue** to scale- up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale- up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we continue to engage third parties to assist us in the commercialization of our medicines, our product revenues and profitability may be lower than if we commercialized such medicines ourselves. If the market does not accept our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, we are not likely to generate substantial revenues or become consistently profitable. Even if our medicines are authorized for marketing, our success will depend upon the medical community, patients and third- party payers accepting our medicines as medically useful, cost- effective, safe and convenient. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. Furthermore, we and our partners may not successfully commercialize additional medicines. Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third- party payers regarding the price we can charge for our medicines, we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third- party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, economically unviable. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has **in the past** disclosed that SPINRAZA revenue ~~has~~ decreased in part due to lower pricing in the U. S. and certain rest **-** of **-** world markets. The degree of market acceptance for our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, depends upon a number of factors, including the: ● receipt and scope of marketing authorizations; ● establishment and demonstration in the medical and patient community of the efficacy and safety of our medicines and their potential advantages over competing products; ● cost and effectiveness of our medicines compared to other available therapies; ● patient convenience of the dosing regimen for our medicines; and ● reimbursement policies of government and third- party payers. Based on the profile of our medicines, physicians, patients, patient advocates, payers or the medical community in general may not accept or use any of the medicines that we **or our partners** may develop. For example, TEGSEDI requires periodic blood and urine monitoring ~~,~~ **and** is available in the U. S. only through a **risk evaluation and mitigation strategy, or** REMS program **. In addition** , ~~and~~ the product label **for TEGSEDI** in the U. S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main **external** competitors in the U. S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or EU, requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines. If ~~we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the ability to conduct periodic blood and urine monitoring of our patients as a result of the COVID-19 pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales. If~~ government or other third- party payers fail to provide adequate coverage and payment rates for our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, our revenue will be limited. In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third- party payers. The majority of patients in the U. S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new medicines when more established or lower cost therapeutic

alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our medicines affordable. Even if favorable coverage status and adequate reimbursement rates are attained, less favorable coverage policies and reimbursement rates may be implemented in the future. Accordingly, **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development ~~,~~ will face competition from other therapies and medicines for limited financial resources. ~~We~~ **Furthermore, we** or our partners may need to conduct post- marketing studies to demonstrate the cost- effectiveness of any future products to satisfy third- party payers. These studies might require us to commit a significant amount of management time and financial and other resources. **In addition,** ~~Third~~ **third** - party payers may never consider our future products as cost-effective ~~.~~ **and** ~~Adequate~~ **adequate** third- party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development. Third- party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U. S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Affordable Care Act, or ACA, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers and continues to significantly impact the U. S. pharmaceutical industry. There have been judicial and Congressional challenges to certain aspects of the ACA, as well as efforts to repeal or replace certain aspects of the ACA. It is unclear how future litigation and healthcare reform measures will impact the ACA and our business. Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U. S. and in international markets. In the U. S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U. S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices, increase competition **(including by enhancing support for generic and biosimilar drugs)** , lower out- of- pocket drug costs for patients, **curtail spread pricing practices by pharmacy benefit managers,** and foster scientific innovation to promote better health care and improved health. In addition, the **Inflation Reduction Act of 2022, or the** IRA, ~~among~~ **includes key actions aimed at reducing** ~~other~~ -- **the** ~~things,~~ **costs of prescription drugs and** allows HHS to negotiate the price of certain single- source drugs covered under Medicare and **establish a price cap on such drugs** ~~imposes rebates under Medicare Part B and Medicare Part D~~ . ~~In~~ **Specifically, in** an effort to curb Medicare patients' out- of- pocket costs for prescription drugs, the Part D redesign legislation **under the IRA** requires **, among other things, (1) a cap on out- of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug** manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. ~~Furthermore~~ **The IRA permits HHS to implement many of these provisions through guidance , as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration' s October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in** any **health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march- in rights under the Bayh- Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March- In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march- in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future. Any** reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to ~~340B~~ covered entities **under the Public Health Service Act 340B drug pricing program** . Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability ~~. Further, the Biden administration released an executive order on October 14, 2022, directing HHS to submit a report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is unclear whether or how this executive order or similar policy initiatives will be implemented in the future~~ . At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. **For example, on January 5, 2024, the FDA approved Florida' s Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs.** Third- party coverage and reimbursement for medicines may not be available or adequate in either the U. S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits. If we or our partners fail to compete effectively, our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, will not generate significant revenues. Our competitors engage in drug

discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. In addition, other companies are engaged in developing RNA- targeted technology. Our competitors may succeed in developing medicines that are: ● priced lower than our medicines; ● reimbursed more favorably by government and other third- party payers than our medicines; ● safer than our medicines; ● more effective than our medicines; or ● more convenient to use than our medicines. These competitive developments could make our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, obsolete or non-competitive. Certain of our partners are pursuing other technologies or developing other medicines either on their own or in collaboration with others, including our competitors, to treat some of the same diseases our own collaborative programs target. Competition may negatively impact a partner' s focus on and commitment to our medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen~~ and ~~tofersen~~ **our medicines in development** . Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products, in obtaining FDA and other regulatory authorizations of such products and in commercializing such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do or more successfully commercialize their products. There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example: ● Onasemnogene abeparvovec and risdiplam compete with SPINRAZA; ● **Taldefgrobep alfa, Evrysdi GYM329 and NMD670 could compete with SPINRAZA; ●** Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and **WAINUA** ~~could compete with eplontersen~~ ; ● Acoramidis **, NTLA- 2001 and NNC6019- 0001** could compete with TEGSEDI and ~~eplontersen~~ **WAINUA** ; ● ARO- APOC3 ~~, lomitapide~~ and pegozafermin could compete with WAYLIVRA and olezarsen; ● Lanadelumab- flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, ~~and~~ **deucrictibant,** NTLA- 2002 **and STAR- 0215** could compete with donidalorsen; ● Olpasiran **, zerlasiran, lepodisiran** and ~~SLN360~~ **muvalaplin** could compete with pelacarsen; ~~and~~ ● NI- ~~204~~ **005 / AP- 101** could compete with ~~tofersen~~ **QALSODY; ● VIR- 2218 PEG- IFN- α, VIR- 3434 ± VIR- 2218 ± PEG- IFN- α, VIR- 2218 BRII- 179, NI- 204VIR- 2218 GS- 9688 nivolumab, AB- 729, imdusiran Peg- IFNa- 2α NA, xalnesiran RG6084 NA, xalnesiran NA, xalnesiran pegIFN NA, xalnesiran RO7049389 NA, xalnesiran ruzotolimod NA, RO7049389 ruzotolimod NA could complete with bepirovirsen; and ● Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibeprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, povetacicept, avacincaptad pegol, pegcetacoplan, tinlarebant, danicopan, GT005, AVD- 104 and ANX007 could compete with IONIS- FB- LRx** . SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries. Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a gene therapy product that was approved in the U. S. in May 2019 and in the EU in May 2020 for the treatment of SMA, as well as risdiplam, an oral product for the treatment of SMA that was approved in the U. S. in August 2020 and in the EU in March 2021. Biogen has **in the past** disclosed that SPINRAZA revenue ~~has~~ decreased ~~primarily~~ due to a reduction in demand as a result of increased competition and that future sales of SPINRAZA may be adversely affected by competing products. Additionally, companies that are developing medicines that target the same patient populations as our medicines in development may compete with us to enroll participants in the clinical trials for such medicines, which could make it more difficult for us to complete enrollment for these clinical trials. Our medicines could be subject to regulatory limitations following approval. Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product' s approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development. The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label and on advertising, promotional and distribution activities. For example: ● in the U. S., TEGSEDI' s label contains a boxed warning for thrombocytopenia and glomerulonephritis; ● TEGSEDI requires periodic blood and urine monitoring; and ● in the U. S., TEGSEDI is available only through a REMS program. Prescription medicines may be promoted only for the approved indication (s) in accordance with the approved label. The FDA and other ~~agencies~~ **regulatory authorities** actively enforce the laws and regulations prohibiting the promotion of off- label uses, and a company that is found to have improperly promoted off- label uses may be subject to significant liability. In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post- approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post- authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post- marketing studies are not satisfactory, the FDA, EC or other foreign regulatory authorities may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill. If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our ~~manufacturers~~ **CMOs** or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and / or change the labeling of our medicines. We depend on our ~~collaboration~~ **collaborations** with Biogen for the development and commercialization of SPINRAZA **and QALSODY** . We have entered into ~~a~~ **separate** collaborative ~~arrangement~~ **arrangements** with Biogen to develop and commercialize SPINRAZA **and QALSODY** . We entered into ~~this~~ **these** ~~collaboration~~ **collaborations** primarily to: ● fund our

development activities for SPINRAZA **and QALSODY** ; ● seek and obtain regulatory approvals for SPINRAZA **and QALSODY** ; and ● successfully commercialize SPINRAZA **and QALSODY** . We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA **and QALSODY** , generate additional clinical data for SPINRAZA **and QALSODY** , manufacture ~~,~~ **SPINRAZA** and ~~continue to~~ **QALSODY, and** successfully commercialize SPINRAZA **and QALSODY** . In general, we cannot control the amount and timing of resources that Biogen devotes to our ~~collaboration~~ **collaborations** . If Biogen fails to further develop SPINRAZA **or QALSODY** , obtain additional regulatory approvals for SPINRAZA **or QALSODY** , manufacture **SPINRAZA** or ~~continue to~~ **QALSODY, or** successfully commercialize SPINRAZA **or QALSODY** , or if Biogen' s efforts in any of these respects are ineffective, revenues for SPINRAZA **or QALSODY** would be negatively affected. In addition, our ~~collaboration~~ **collaborations** with Biogen may not continue for various reasons. Biogen can terminate our ~~collaboration~~ **collaborations** at any time. If Biogen stops developing or commercializing SPINRAZA **or QALSODY** , we would have to seek or spend additional funding, and SPINRAZA' s **or QALSODY' s** commercialization may be harmed ~~or delayed~~ . We depend on our collaboration with AstraZeneca for the joint development and commercialization of ~~eplontersen~~ **WAINUA** . We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize ~~eplontersen~~ **WAINUA** . Under the terms of the collaboration agreement, we and AstraZeneca will co- develop and co- commercialize ~~eplontersen~~ **WAINUA** in the U. S. and AstraZeneca will have the sole right to commercialize ~~eplontersen~~ **WAINUA** in all other countries ~~, except for certain Latin American countries. Prior to co- commercializing eplontersen in the U. S., we will need to negotiate a co- commercialization agreement with AstraZeneca to govern the parties' performance of co- commercialization, which agreement will include a commercial plan and budget~~ . As a company we do not have experience with co- commercialization arrangements. We also do not have control over the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U. S. If the co- commercialization arrangement for ~~eplontersen~~ **WAINUA** is not successful for any reason, ~~eplontersen~~ **WAINUA** may not meet our commercial objectives and our revenues for ~~eplontersen~~ **WAINUA** may be limited. In addition, a Joint Steering Committee, or JSC, having equal membership from us and AstraZeneca, and various subcommittees oversee and coordinate the development, manufacturing, commercialization and other exploitation activities for ~~eplontersen~~ **WAINUA** in the U. S. by mutual agreement. If any subcommittee cannot reach unanimous agreement on any matter within its respective scope of authority, such matter may be referred to the JSC for resolution. If the JSC cannot come to a mutual agreement on any particular matter, this could delay our ability to develop or commercialize ~~eplontersen~~ **WAINUA** . If we are not successful in expanding our manufacturing capabilities or cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably. To successfully commercialize any of our medicines, we need to optimize and manage large- scale commercial manufacturing capabilities either on a standalone basis or through a third- party manufacturer. As our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. **While** ~~To that end,~~ we ~~have begun work on a new~~ **believe our current capabilities and those we obtain through third- party manufacturers support our** manufacturing **needs now** ~~facility in Oceanside~~ , **it** ~~California that~~ will **be important to** expand our manufacturing infrastructure ~~. We~~ **in the future, which** will ~~incur~~ **likely require** substantial expenditures ~~to build our new manufacturing facility and, following its completion, will likely need to hire and train additional staff to operate the facility~~ . If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future. In addition, we have limited experience manufacturing pharmaceutical products of the chemical class represented by our medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We or our partners may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products. Manufacturers, including us, must adhere to the FDA' s cGMP regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners and our contract manufacturers may not comply or maintain compliance with cGMP, or similar foreign regulations. Non- compliance could significantly delay or prevent receipt of marketing authorizations for our medicines, including authorizations for **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ and our medicines in development. We rely on third- party manufacturers to supply the drug substance and drug product for TEGSEDI and **WAINUA and** drug product for WAYLIVRA. Any delays or disruption to our own or third- party commercial manufacturing capabilities ~~, including any interruption to our supply chain as a result of the COVID- 19 pandemic or the ongoing war between Russia and Ukraine,~~ could limit the commercial success of our medicines ~~. We are relying on third parties to market, sell and distribute TEGSEDI and WAYLIVRA. We have entered into agreements with third parties to commercialize TEGSEDI and WAYLIVRA as follows: ● In April 2021, we entered into a distribution agreement with Sobi to commercialize TEGSEDI in the U. S. and Canada; ● In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe; and ● In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. We are relying on Sobi and PTC to effectively market, sell and distribute TEGSEDI and WAYLIVRA and have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the COVID- 19 pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in the U. S., Canada, Europe, Latin America or certain Caribbean countries, which could adversely affect our business, prospects, financial condition and results of operations~~ . Risks Related to the Development and

Regulatory Approval of our Medicines If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA~~ , we or our partners cannot sell them in the applicable markets. We cannot guarantee that any of our medicines will be considered safe and effective or will be approved for commercialization. In addition, it is possible that **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA~~ may not be approved in additional markets or for additional indications. We and our partners must conduct time- consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our medicines before they can be approved or receive additional approvals for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries. We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory ~~agencies~~ **authorities** will not approve our medicines for marketing or ~~SPINRAZA, TEGSEDI or~~ **our** ~~WAYLIVRA~~ **commercial medicines** in additional markets or for additional indications. If the FDA or another regulatory ~~agency~~ **authority** believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA,~~ or our medicines in development, the ~~agency~~ **authority** will not approve the specific medicine or will require additional studies, which could be time consuming and expensive and delay or harm commercialization of the medicine. For example, in August 2018 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a **Notice of Non-Compliance Withdrawal Letter, or** Non- W **,** from Health Canada for WAYLIVRA in November 2018. The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a medicine for many reasons, including: ● such authorities may disagree with the design or implementation of our clinical studies; ● we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a medicine is safe and effective for any indication; ● such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the U. S.; ● we or our partners may be unable to demonstrate that our medicine' s clinical and other benefits outweigh its safety risks to support approval; ● such authorities may disagree with the interpretation of data from preclinical or clinical studies; ● such authorities may find deficiencies in the manufacturing processes or facilities of third- party manufacturers who manufacture clinical and commercial supplies for our medicines ~~, or may delay the inspection of such facilities due to restrictions related to the COVID- 19 pandemic~~ ; and ● the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval. Failure to receive marketing authorization for our medicines **in development** , or failure to receive additional marketing authorizations for ~~SPINRAZA, TEGSEDI or~~ **our** ~~WAYLIVRA~~ **commercial medicines** , or delays in these authorizations, could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales. If the results of clinical testing indicate that any of our medicines are not suitable for commercial use, we may need to abandon one or more of our drug development programs. Drug discovery and drug development have inherent risks and the historical failure rate for drugs is high. Antisense medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines are safe and effective for human use in the intended indication (s), we may need to abandon one or more of our drug development programs. Even if our medicines are successful in preclinical and human clinical studies, the medicines may not be successful in late- stage clinical studies. Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies. If any of our medicines in Phase 3 clinical studies ~~, including the studies of donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen,~~ do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline. In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that ~~tofersen~~ **QALSODY** did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring ~~tofersen~~ **QALSODY** were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington' s disease based on the results of a pre- planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines ~~, including the studies of donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen~~ . There are a number of factors that could cause a clinical study to fail or be delayed, including: ● the clinical study may produce negative or inconclusive results; ● regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements; ● we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects or lack of efficacy in the trial; ● we or our partners may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies; ● enrollment in our clinical studies may be slower than we anticipate; ● we or our partners, including our independent clinical investigators, contract research organizations and other third- party service providers on which we rely, may not identify, recruit ~~and~~ **or** train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study; ● the institutional review board for a prospective site might withhold or delay its approval for the study; ● people who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues; ● a clinical study site may deviate from the protocol for the study; ● the cost of our clinical studies may be greater than we anticipate; ● our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and ● the supply or quality of our medicines or other materials necessary to conduct our clinical studies may

be insufficient, inadequate or delayed. **Further** ~~The COVID- 19 pandemic could make some of these factors more likely to occur. In addition, our current medicines, including SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA or other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example~~ , the FDA or other regulatory ~~agencies~~ **authorities** could request, among other things, additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post- approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post- authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. ~~We~~ **In addition, under accelerated approval the FDA is requiring completion of the ongoing Phase 3 trial for QALSODY to confirm the clinical benefit of QALSODY. Moreover, our commercial medicines are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could** have **,** ~~ongoing post- marketing studies for~~ **or** ~~WAYLIVRA and TEGSEDI and~~ **be perceived by a regulatory authority to have,** an ~~EAP for WAYLIVRA~~ **impact on a different medicine we are developing** . **This** ~~Adverse events or results from these studies or the EAPs~~ could ~~negatively impact~~ **cause the FDA** ~~our~~ **or other regulators to ask questions** ~~pending or future marketing approval applications for~~ **or** ~~WAYLIVRA and TEGSEDI in patients with FCS~~ **take actions that could harm or delay** ~~or~~ **our ability to develop and** ~~ATTRv- PN, respectively, or the commercial~~ **commercialize** ~~opportunity for WAYLIVRA or~~ **our** ~~TEGSEDI~~ **medicines or increase our costs** . Any failure or delay in our clinical studies ~~, including the studies of donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen,~~ could reduce the commercial potential or viability of our medicines. We depend on third parties to conduct clinical studies for our medicines and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans. We depend on independent clinical investigators, contract research organizations and other third- party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including **WAINUA for the treatment of ATTR- CM,** donidalorsen, ~~eplontersen, ION363,~~ olezarsen, ~~pelacarsen~~ **ulefnersen** and ~~tofersen~~ **zilganersen** . We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees, but we are responsible for ensuring that such investigators conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. For example, some of our key vendors ~~are~~ **have in the past** ~~experiencing~~ **experienced** labor shortages, which ~~could impact~~ **impacted** their ability to perform services for us for certain of our clinical trials. ~~The~~ **Subsequent** ~~failure~~ **failures** of these third parties to carry out their obligations ~~, including as a result of delays or disruptions caused by the COVID- 19 pandemic~~ , or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines ~~or additional marketing authorizations for TEGSEDI and WAYLIVRA~~ . In addition, while we do not have any clinical trial sites in Ukraine **or Gaza** , we do have a limited number of clinical trial sites in Russia and **Israel** ~~surrounding countries~~ that may be **materially** impacted by the ongoing ~~war~~ **wars** between Russia and Ukraine **and military conflicts in Israel and the surrounding areas, as well as related political or economic responses and counter- responses by various global actors, or collectively, conflicts in Eastern Europe and the Middle East,** and could result in difficulties enrolling or completing our clinical trials in such areas on schedule. Furthermore, the U. S. and its European allies have imposed significant sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. The U. S. government has also indicated it will consider imposing additional sanctions and other similar measures in the future. Our ability to conduct clinical trials in Russia may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, and could increase our costs and delay the clinical development of certain of our medicines. Since corporate partnering is a significant part of our strategy to fund the advancement and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs. To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize some of our unpartnered medicines. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our medicines could suffer. Our corporate partners are developing and funding many of the medicines in our development pipeline. For example, we are relying on: ● AstraZeneca for the joint development and funding of ~~eplontersen~~ **WAINUA** ; ● Novartis for development and funding of pelacarsen; ● ~~Biogen~~ **GSK** for development and funding of ~~tofersen~~ **bepirovirsen** ; **and** ● **Roche** ~~Biogen for additional studies of SPINRAZA; and ● GSK~~ for development and funding of ~~bepirovirsen~~ **IONIS- FB- LRx** . If any of these pharmaceutical companies stops developing and funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively. Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development and commercial programs. In addition to receiving funding, we enter into collaborative arrangements with third parties to: ● conduct clinical studies; ● seek and obtain marketing authorizations; and ● manufacture and commercialize our

medicines. Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Biogen, GSK, Novartis, **Otsuka** and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we anticipated. For example, a collaborator such as AstraZeneca, Biogen, GSK, Novartis, **Otsuka** or Roche, could determine that it is in its financial interest to: ● pursue alternative technologies or develop alternative products that may be competitive with the medicine that is part of the collaboration with us; ● pursue higher- priority programs or change the focus of its own development programs; or ● choose to devote fewer resources to our medicines than it does to its own medicines. If any of these occur, it could affect our partner' s commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including **QALSODY,** SPINRAZA, ~~eplontersen~~ **WAINUA** , **bepirovirsen, donidalorsen, IONIS- FB- LRx and** pelacarsen ~~and tofersen~~ . We may not be able to benefit from orphan drug designation for our medicines. In the U. S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200, 000 individuals in the U. S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user- fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to ~~eplontersen~~ **olezarsen** for the treatment of patients with ~~transthyretin~~ **FCS, to ulefnersen for the treatment of patients with FUS** - ~~mediated amyloidosis~~ **ALS,** and to ION582 for the treatment of patients with Angelman syndrome. The FDA and EMA have granted orphan drug designation to **WAINUA for the treatment of patients with ATTR, to donidalorsen for the treatment of patients with HAE, to** TEGSEDI for the treatment of patients with ATTRv- PN, to WAYLIVRA for the treatment of patients with FCS, ~~and~~ to tominersen for the treatment of patients with HD **, and to ION356 for the treatment of patients with Pelizaeus- Merzbacher disease** . In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine. Risks Associated with our Businesses as a Whole Risks related to our financial condition If we fail to obtain timely funding, we may need to curtail or abandon some of our programs. Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the **expansion** ~~build- out~~ of **our** ~~a new~~ manufacturing ~~facility~~ **capabilities** . All of these activities will require significant cash. As of December 31, ~~2022~~ **2023** , we had cash, cash equivalents and short- term investments equal to $ 2. ~~0~~ **3** billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA~~ , or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors such as: ● successful commercialization of **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA~~ ; ● the profile and launch timing of our medicines **in development** ~~, including donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen~~ ; ● changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements; ● continued scientific progress in our research, drug discovery and development programs; ● the size of our programs and progress with preclinical and clinical studies; ● the time and costs involved in obtaining marketing authorizations; ● competing technological and market developments, including the introduction by others of new therapies that address our markets; and ● our manufacturing requirements and capacity to fulfill such requirements. If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available on acceptable terms or at all. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs **, or commercial operations** . Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or medicines. We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future. Because drug discovery and development require substantial lead- time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of approximately $ 1. ~~4~~ **8** billion and stockholders' equity of approximately $ 0. ~~6~~ **4** billion ~~. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations~~ . Most of our income has historically come from collaborative arrangements, including commercial revenue from royalties and R & D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability. We may not be entitled to obtain additional milestone payments under our royalty monetization agreement with Royalty Pharma. In January 2023, we entered into a Royalty Purchase Agreement with Royalty Pharma Investments. In addition to the $ 500 million we received at closing, this agreement makes available to us up to an additional $ 625 million in milestone payments. However, these additional

milestone payments are subject to satisfaction of certain conditions related to the regulatory approval or commercial sales of pelacarsen, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or if we fail to meet our obligations or default under this agreement, the actual amount of additional payments to us could be substantially less than the maximum amounts available thereunder. Risks related to our intellectual property If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us. Our success depends to a significant degree upon whether we can continue to develop, secure and maintain intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U. S. or in other countries and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights, any of which could impact our ability to compete effectively. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source. We cannot be certain that the U. S. Patent and Trademark Office, or U. S. PTO, and courts in the U. S. or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen~~ , or any of our medicines in development **,** as patentable. Method- of- use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off- label. Although off- label prescriptions may infringe or contribute to the infringement of method- of- use patents, the practice is common and such infringement is difficult to prevent, even through legal action. If we or any licensor partner loses or cannot obtain patent protection for **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen,~~ or any of our medicines in development, it could have a material adverse impact on our business. Intellectual property litigation could be expensive and prevent us from pursuing our programs. From time to time, we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U. S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. If a third party claims that our medicines or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the U. S. are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain. Risks related to product liability We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all. Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to **our commercial medicines** ~~SPINRAZA, TEGSEDI and WAYLIVRA,~~ and our medicines in development. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our medicines, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material. Risks related to our personnel The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success. We are dependent on the principal members of our management and scientific staff, and as we move towards commercializing medicines on our own, we will become increasingly dependent on the principal members of our commercial team. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our management, key scientific or commercial employees might slow the achievement of important research and development or commercial goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work **and that we recruit and retain qualified marketing, sales, market access, distribution, and related personnel to commercialize our medicines** . We may not be able to attract and retain skilled and experienced ~~scientific~~ personnel on acceptable terms because of intense competition for experienced ~~scientists~~ **personnel** among many pharmaceutical and health care companies, universities and non- profit research institutions. In addition, failure to succeed in clinical studies **or in commercializing our medicines** may make it more challenging to recruit and retain qualified ~~scientific~~ personnel. Risks related to ~~the COVID- 19 pandemic~~ **pandemics , climate change** and other events Our business may be adversely affected by pandemics, climate change, extreme weather events, earthquakes, ~~war~~ **wars** , civil or political unrest, terrorism or other catastrophic events. Our business could be adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause disruption in the operations of third- party manufacturers and contract research organizations upon whom we rely. For example, **enrollment in** some **of our clinical trials** ~~physician and hospital policies that were put in place as~~ **was** ~~a result of~~ **delayed due to** the COVID- 19 pandemic ~~restricted in- person access by third parties, which in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. In addition, in December 2021, Novartis announced that enrollment for the Phase 3~~

~~HORIZON study had been delayed due to the COVID- 19 pandemic. The COVID- 19 pandemic continues to evolve, and while we believe we have not experienced material adverse effects to our business as a result of the COVID- 19 pandemic, the ultimate impact of the COVID- 19 pandemic or a similar health epidemic is highly uncertain~~ . In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we currently manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California ~~and will move such manufacturing to our new facility in Oceanside, California once it is built~~ . We manufacture the finished drug product for TEGSEDI **, WAINUA** and WAYLIVRA at third- party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA **and QALSODY** . The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, ~~war~~ **wars** , civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U. S. government, including the FDA. Risks related to cybersecurity **, social media and artificial intelligence** We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks. We are dependent upon our own and third- party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber- attacks are increasing in their frequency, sophistication and intensity, ~~with third- party phishing and social engineering attacks in particular~~ **particularly** ~~increasing~~ **as companies (including us) moved to more remote work structures** during **and following** the COVID- 19 pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing ~~war between Russia~~ **conflicts in Eastern Europe** and **the Middle East** ~~Ukraine, as a result of which several companies (not including us) have reported recent cybersecurity events~~ . Cyber- attacks could include the deployment of harmful malware, denial- of- service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation **, delay progress on the development of our medicines** , compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions or identify breaches in our systems that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us **. The increasing use of social media platforms and artificial intelligence based software presents new risks and challenges. Social media is increasingly being used to communicate about our medicines and the diseases our therapies are designed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear and create uncertainty and risk of noncompliance with regulations applicable to our business. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on social media. We may also encounter criticism on social media regarding our company, management, or medicines. Our reputation could be damaged by negative publicity or if adverse information concerning us is posted on social media platforms or similar mediums, which we may not be able to reverse. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business. Additionally, the use of artificial intelligence, or AI, based software is increasingly being used in the biopharmaceutical industry. Use of AI based software may lead to the release of confidential proprietary information, which may impact our ability to realize the benefit of our intellectual property** . Risks related to our securities and the global credit markets If we do not progress in our programs as anticipated, the price of our securities could decrease. For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control ~~, including the impacts of the COVID- 19 pandemic~~ . If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related

to **our commercial medicines** ~~SPINRAZA, TEGSEDI, WAYLIVRA, donidalorsen, eplontersen, ION363, olezarsen, pelacarsen~~ and ~~tofersen~~ **medicines in development** , the price of our securities could decrease. If the price of our securities continues to be highly volatile, this could make it harder to liquidate your investment and could increase your risk of suffering a loss. The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, ~~2022~~ **2023** , the **closing** market price of our common stock ranged from $ ~~48~~ **52** . ~~82~~ **27** to $ ~~28~~ **32** . ~~25~~ **69** per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines. Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, **recent events such as** the COVID- 19 pandemic **, the ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank have** caused ~~a significant disruption~~ **disruptions** of global financial markets and resulted in increased volatility in the trading price of our common stock ~~. The global credit and financial markets may also be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto~~ . In addition, industry factors may materially harm the market price of our common stock. Nasdaq, and the market for biotechnology companies in particular, have historically experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies that investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations. Provisions in our certificate of incorporation **, bylaws** , convertible notes documents, call spread hedge transaction documents and Delaware law may prevent stockholders from receiving a premium for their shares. Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2 / 3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met. Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, ~~chairman~~ **chairperson** of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders. The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then- current market prices. In ~~April~~ **2023, we completed a $ 575 million offering of 1. 75 % Notes and used $ 488. 2 million of the net proceeds from the issuance of the 1. 75 % Notes to repurchase $ 504. 4 million of our 0. 125 % Notes. In** 2021, we completed a $ 632. 5 million offering of 0 % Notes and used a portion of the net proceeds from the issuance of the 0 % Notes to repurchase $ 247. 9 million of our 1 % Notes for $ 257. 0 million. In ~~December~~ 2019, we entered into privately negotiated exchange and / or subscription agreements with certain new investors and certain holders of our existing 1 % Notes to exchange $ 375. 6 million of our 1 % Notes for $ 439. 3 million of our 0. 125 % Notes, and to issue $ 109. 5 million of our 0. 125 % Notes. Additionally, in connection with the pricing of our 0 % Notes and 0. 125 % Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser. These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then- current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. Future sales of our common stock in the public market could adversely affect the trading price of our securities. Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, **as of December 31, 2023,** we may issue approximately ~~17~~ **28** . ~~5~~ **2** million shares of our common stock upon conversion of our **1. 75 % Notes,** 0 % Notes and 0. 125 % Notes **. In connection with the issuance of the 0 % Notes and 0. 125 % Notes** , ~~up to~~ **we entered into certain call spread transactions covering** 10. 9 million shares **and 6. 6 million shares, respectively, that we expect will offset the dilution to holders of common stock upon any conversion of those notes. In addition, of the shares reserved, 6. 1 million shares are reserved for issuance upon conversion of 0. 125 % Notes that we have repurchased and are currently held by us in treasury (and thus would not be dilutive). As a result, to the extent we elect to convert the 0. 125 % Notes held by us in treasury, we expect we would receive up to 6. 1 million shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 0. 125 % Notes held in treasury). However, the anti- dilutive effect of the convertible note hedges is offset by certain warrant transactions we entered into** in connection with

the ~~warrant transactions we entered into in connection with the~~ issuance of ~~our~~ **the** 0 % Notes ~~,~~ and ~~up to 6. 6 million shares in connection with~~ the ~~warrant transactions we entered into in connection with the issuance of our~~ 0. 125 % Notes ~~, in each case subject to customary anti- dilution adjustments~~. The addition of any of these shares into the public market may have an adverse effect on the price of our securities. In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0 % Notes and 0. 125 % Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over- the- counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0 % Notes or 0. 125 % Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0 % Notes or 0. 125 % Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants. Negative conditions in the global credit markets and financial services and other industries may adversely affect our business **, financial condition or stock price**. The global credit **and financial** markets **have experienced extreme volatility** ~~, the financial services industry, the U. S. capital markets,~~ and **disruptions recently, including** ~~the U. S. economy~~ as a **result of** ~~whole have recently experienced substantial turmoil and uncertainty characterized by unprecedented intervention by the U. S. federal government in response to~~ the COVID- 19 pandemic ~~. While~~ **, ongoing conflicts in Eastern Europe and** the ~~potential~~ **Middle East, and the failure of Silicon Valley Bank. These disruptions can result in severely diminished liquidity and credit availability, declines in consumer confidence, declines in** economic **growth** ~~impact brought by~~ **, increases in unemployment rates** and **uncertainty about economic stability. There can** ~~the duration of, the COVID- 19 pandemic may~~ be ~~difficult to assess or~~ **no assurance that further deterioration in** ~~predict~~ **credit and** ~~, it could result in significant disruption of global~~ financial markets **and confidence in economic conditions will not occur. If the current equity and credit markets deteriorate** , ~~reducing~~ **it may make any necessary debt** ~~our~~ **or** ~~ability to access capital~~ **equity financing more difficult** , ~~which~~ **more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms** could ~~in the future negatively~~ **have a material adverse** ~~affect~~ **effect on our operations, growth plans, financial performance** ~~our~~ **or** ~~liquidity~~ **stock price**. In addition ~~, a recession or market correction resulting from the spread of COVID- 19 could materially affect our business and has and could continue to affect the value of our securities. In addition, the global credit and financial markets may be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto. In the past, the failure, bankruptcy, or sale of various financial and other institutions created similar turmoil and uncertainty in such markets and industries. It is possible that a similar crisis in the global credit markets, the U. S. capital markets, the financial services industry or the U. S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. Additionally~~, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all ~~. In addition, due to the rapidly rising inflation rate, we may experience significantly increased costs of goods and services for our business~~. A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business. In addition to our U. S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations, we are subject to numerous risks associated with international business activities, including: ● compliance with differing or unexpected regulatory requirements for our medicines and foreign employees; ● complexities associated with managing multiple payer reimbursement regimes, government payers or patient self- pay systems; ● difficulties in staffing and managing foreign operations; ● in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third- party distributors or strategic partners; ● foreign government taxes, regulations and permit requirements; ● U. S. and foreign government tariffs, trade **and export** restrictions, price and exchange controls and other regulatory requirements; ● anti- corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions; ● economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics ~~, such as the COVID- 19 pandemic~~, in particular foreign countries or globally; ● fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country; ● compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad; ● workforce uncertainty in countries where labor unrest is more common than in the U. S.; and ● changes in diplomatic and trade relationships. Our business activities outside of the U. S. are subject to the FCPA and similar anti- bribery or anti- corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom' s Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third- party business partners (including our **contract research organizations, contract manufacturing organizations,** distributors, wholesalers, agents, contractors and other partners) will comply with anti- bribery laws. **Importantly** ~~In particular~~, we do not control the actions of manufacturers and other third- party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have an adverse impact on our business and financial condition. Risks related to compliance with laws Our operations are subject to ~~additional~~ **extensive legal and regulatory requirements affecting the** ~~healthcare~~ ---- **health** ~~laws~~ **care industry**. Our operations are subject to ~~additional~~ **extensive legal**

and regulatory requirements affecting the ~~healthcare~~ ---- **health** ~~laws~~ **care industry** , including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings. Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected. Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store most of these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause: ● interruption of our research, development and manufacturing efforts; ● injury to our employees and others; ● environmental damage resulting in costly clean up; and ● liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products. In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance for pollution liability in amounts and types that we consider commercially reasonable, the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected. Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance. Each year we are required to evaluate our internal control systems to allow management to report on **,** and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes- Oxley Act. As a result, we continue to incur additional expenses and divert our management' s time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock. The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. In July 2010, the Dodd- Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd- Frank Act related to " say on pay " and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which has and may in the future lead to additional compliance costs and impact the manner in which we operate our business. Risks related to taxes Our ability to use our net operating loss carryovers and certain other tax attributes may be limited. Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under the Code, we can ~~carryforward~~ **carry forward** our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits. Under the current U. S. federal income tax law, U. S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U. S. federal NOLs is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U. S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes. In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an " ownership change, " which is generally defined as a greater than 50 percentage- point cumulative change, by value, in its equity ownership over a three- year period, the corporation' s ability to use its pre- change NOL carryforwards and other pre- change tax attributes to offset its post- change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of **our merger with Akcea Therapeutics, Inc. in 2020, or** the Akcea Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea' s pre- merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre- merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of **NOLs** ~~net operating losses~~ is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. Our future taxable income could be impacted by changes in tax laws, regulations and treaties. A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us. We could be subject to additional tax liabilities. We are subject to U. S. federal, state, local and foreign income taxes, sales taxes in the U. S., withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign

currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value- added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.