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

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

The following risk factors and other information included in this Annual Report on Form 10- K should be carefully considered. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10- K for a discussion of some of the forward- looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. Risks Related to the Discovery, Development, and Commercialization of our Products and Product Candidates If we do not successfully commercialize PYRUKYND ® and other products for which we receive approval, our prospects may be substantially harmed. ~~In February 2022, we obtained marketing approval from the FDA for~~ PYRUKYND ® (mitapivat) **is approved for use by the FDA** for the treatment of hemolytic anemia in adults with PK deficiency in the United States **and by** ~~. In November 2022, we received marketing authorization from~~ the European Commission for ~~PYRUKYND ® for~~ the treatment of PK deficiency in adult patients in the EU **. Additionally,** ~~and in December 2022~~ we received marketing authorization in Great Britain for PYRUKYND ® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. **In December 2024, we announced that we submitted an sNDA, to the FDA for** PYRUKYND ® ~~is~~ **for** the ~~first product in~~ **treatment of adult patients with non- transfusion dependent and transfusion- dependent alpha-** ~~our~~ **or** ~~rare disease portfolio~~ **beta- thalassemia, which was accepted with standard review and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced** that ~~has received marketing approval~~ **we submitted a MAA to the EMA,** and ~~is~~ **regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND ® for the treatment of adult patients with non- transfusion dependent and transfusion- dependent alpha-** ~~our~~ **or beta- thalassemia** ~~first product following the sale of our oncology business to Servier in March 2021~~ . Our ability to generate meaningful revenue from PYRUKYND ® will depend heavily on our successful development and commercialization of the product. **We generated $ 36. 5 million, $ 26. 8 million and $ 11. 7 million of net product revenues from sales of PYRUKYND ® in the years ended December 31, 2024, 2023 and 2022, respectively.** In connection with our regulatory ~~approvals~~ **approval** in the EU and Great Britain, we are currently providing access to PYRUKYND ® **on a** free of charge **basis** for eligible patients in those jurisdictions through a global managed access program **. We provide access to PYRUKYND ® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. Beyond the global managed access program, we continue to evaluate options for the commercialization of PYRUKYND ® outside of the United States, including through exploring potential partnership opportunities, such as the NewBridge Agreement** . The development and commercialization of PYRUKYND ® could be unsuccessful if: • the medical community and third- party payors do not accept PYRUKYND ® as safe, efficacious and cost- effective ~~for the treatment of adults with PK deficiency~~ in the approved jurisdictions; • we fail to maintain the necessary financial resources and expertise to manufacture, market and sell PYRUKYND ®; • we fail to develop, implement and maintain effective marketing, sales and distribution strategies and operations for the development and commercialization of PYRUKYND ®; • we fail to continue to develop, validate and maintain a commercially viable manufacturing process for PYRUKYND ® that is compliant with current good manufacturing practices, or cGMP; • we fail to successfully obtain third party reimbursement and generate **and sustain** commercial demand that results in expected sales of PYRUKYND ®; • PYRUKYND ® ~~may become~~ **becomes** subject to unfavorable pricing regulations and third- party reimbursement practices; • we encounter any third- party patent interference, derivation, inter partes review, post- grant review, reexamination or patent infringement claims with respect to PYRUKYND ®; • we fail to comply with regulatory and legal requirements applicable to the sale of PYRUKYND ®; • competing drug products are approved for the same indications as PYRUKYND ®; • significant safety, manufacturing and / or quality risks are identified; • PYRUKYND ® fails to gain and / or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community; • a significant number of eligible patients with PK deficiency are not prescribed PYRUKYND ® and, if they are, such patients do not stay on treatment; or • PYRUKYND ® does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in other indications. If we experience significant delays or an inability to successfully develop and commercialize PYRUKYND ® **,** our business would be materially harmed. We depend heavily on the success of our clinical- stage product candidates, including the potential approval of PYRUKYND ® for ~~use in indications other~~ **the** ~~than PK deficiency~~ **treatment of thalassemia or SCD in the United States** and in other jurisdictions. Clinical trials of our product candidates may not be successful for a number of important reasons. If we or our collaborators are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed. We have invested a significant portion of our efforts and financial resources in the identification of our product candidates and the development of our most advanced clinical programs, including PYRUKYND ® **and tebapivat** . Our ability to generate meaningful product revenue will depend heavily on the successful clinical development and eventual commercialization of our current and any future product candidates, including PYRUKYND ®. ~~While~~ **In December 2024,** we ~~obtained marketing approval of~~ **announced that we submitted an sNDA to the FDA for** PYRUKYND ® for the treatment of ~~hemolytic anemia in adults~~ **adult patients** with ~~PK deficiency~~ **non- transfusion dependent and transfusion- dependent alpha- or beta- thalassemia, which was accepted with standard review and granted a PDUFA goal date of September 7, 2025. Also** in **December 2024, we announced that we submitted**

an MAA to the **EMA and regulatory applications to the Kingdom of Saudi Arabia and** United ~~States and marketing~~ **Arab Emirates health** ~~authorization~~ -- **authorities** ~~of~~ **for** PYRUKYND ® for the treatment of ~~adults~~ - **adult patients** with **non-transfusion dependent** ~~PK deficiency in the EU~~ and ~~Great Britain, we~~ **transfusion- dependent alpha- or beta- thalassemia. We** cannot be certain that we will obtain marketing approval of PYRUKYND ® in **thalassemia in such** ~~indications~~ - **jurisdictions , nor can we be certain that we will obtain marketing approval of PYRUKYND ® for any** other **indication** ~~than PK deficiency~~ or in other jurisdictions. We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements in foreign jurisdictions. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including: • we, or our collaborators, may fail to demonstrate efficacy in a clinical trial or across a broad population of patients; • it is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. For example, many compounds that initially showed promise in earlier stage testing for treating specific indications have later been found to cause side effects that prevented further development of the compound; • our product candidates may have undesirable side effects or other unexpected characteristics or otherwise expose participants to unacceptable health risks, causing us, our collaborators or our investigators, regulators or institutional review boards or the data safety monitoring board for such trial to halt, delay, interrupt, suspend or terminate the trials or cause us, or any collaborators, to abandon ~~development~~ or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective; • if our product candidates have undesirable side effects, it could result in a more restrictive label **or the addition of safety warnings** , or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities **. For example, in January 2025, the USPI for PYRUKYND ® for the treatment of hemolytic anemia in adults with PK deficiency was updated to include information regarding hepatocellular injury observed in clinical trials in patients with thalassemia treated with PYRUKYND ® at a higher dose than recommended for patients with PK deficiency** ; • clinical trials of our product candidates may produce negative or inconclusive results, and we, or our collaborators, may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs; • regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site; • we or our collaborators may have delays in reaching or ~~fail~~ **failing** to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites; • the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the orphan diseases we target in our rare disease programs, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate; • third- party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all; • significant preclinical study or clinical trial delays could shorten any periods during which we, or any collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do; • the cost of clinical trials of our product candidates may be greater than anticipated; and • the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate. In December 2016, we withdrew our IND for AG- 519, our second PK activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug- induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG- 519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing clinical trials for PYRUKYND ® ~~, our~~ - **or tebapivat** ~~first PK activator~~ , we cannot provide any assurances that there will not be other treatment-related severe adverse events in our other clinical trials, or that our other trials will not be placed on clinical hold in the future. Our failure to successfully begin and complete clinical trials of our product candidates **,** and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates **,** could result in additional costs to us, or any collaborators, **and** would impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties **,** and would significantly harm our business. We may engage in in- licensing transactions or acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources. We have and may in the future enter into additional transactions to in- license products, technologies or assets or to acquire other products, technologies, assets or businesses. As part of the evolution of our research organization, we plan to prioritize in- licensing or acquiring assets for future pipeline growth. For example, in July 2023, we entered into a license agreement with Alnylam for the development and commercialization of products containing or comprised of an siRNA development candidate discovered by Alnylam and targeting the TMPRSS6 gene, and we ~~intend to pursue~~ **have begun preclinical** development of a ~~licensed~~ product **candidate** for the potential treatment of **patients with** PV. Our ability to successfully in- license or acquire assets and develop product candidates following such transactions is unproven. If we do identify additional suitable candidates or assets for in-licensing transactions or acquisitions, we may not be able to make such transactions on favorable terms, or at all. Such

transactions may require us to relinquish rights to develop product candidates in certain indications, limit our ability to pursue certain targets or require us to make significant milestone or royalty payments to third parties upon achievement of certain events. For example, we are responsible to pay up to $ 130. 0 million in potential development and regulatory milestones, in addition to sales milestones as well as tiered royalties on annual net sales, if any, of any licensed products, under the license agreement with Alnylam. Further, any in- licensing transaction or acquisitions we undertake may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or an in- licensing transaction or issue our common stock or other equity securities to the stockholders of the counterparty, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business, product or technology that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non- disruptive manner. Such transactions may also divert management attention from day- to- day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot ensure that following any transaction we would achieve the expected synergies to justify the transactions. We cannot predict the number, timing or size of future transactions or the effect that any such transactions might have on our operating results. Public health epidemics or pandemics may affect our ability to initiate or continue our planned, ongoing and future preclinical studies and clinical trials, disrupt regulatory activities, disrupt our ability to maintain a commercial infrastructure for our product or have other adverse effects on our business and operations. ~~Public health emergencies or pandemics could adversely affect our business, financial condition, results of operations, and prospects.~~ We may face delays, disruptions or shortages as a result of ~~such~~ **public health epidemics or** pandemics that may affect our ability to initiate and complete preclinical studies and clinical trials or impact our commercialization efforts. We have **previously** experienced disruptions to certain clinical and research activities at our contract research organizations, or CROs, due to the ~~recent~~ COVID- 19 pandemic. Any future pandemic or public health emergency could result in **delays or pauses in** site initiation, participant recruitment and enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis ~~being paused or delayed~~ due to changes in hospital or university policies, federal, state or local regulations, diversion of hospital resources or other reasons related to a public health emergency. If a pandemic or public health emergency arises in the future, we may face difficulties recruiting or retaining patients in our ongoing clinical trials, and patients enrolled in our clinical trials may be unable or unwilling to visit clinical trial sites which may impact the collection of important clinical trial data and may necessitate remote data verification. In addition, limitations on the ability to visit sites may affect our enrollment timelines for our clinical trials, and may adversely affect the timing of completion of our clinical trials or our ability to complete clinical trials in a fully compliant manner. Additionally, the potential suspension of clinical trial activity at clinical trial sites or reduced availability of CRO personnel may have an adverse impact on our clinical trial plans and timelines. ~~The public health emergency declarations related to COVID- 19 ended on May 11, 2023. The FDA ended a number of COVID- 19 related policies and retained a number of COVID- 19 related policies. It is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates.~~ We cannot be certain what the overall impact of future health emergencies or pandemics will be on our business. If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented. We or our collaborators may not be able to initiate, continue or complete clinical trials for our product candidates if we or they are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States ~~. Furthermore, enrollment had previously been particularly challenging in light of the recent COVID- 19 pandemic~~ . Patient enrollment is also affected by other factors including: • prevalence and severity of the disease under investigation; • availability and efficacy of approved medications for the disease under investigation; • eligibility criteria for the study in question; • perceived risks and benefits of the product candidate under study; • efforts to facilitate timely enrollment in clinical trials; • patient referral practices of physicians; • the ability to monitor patients adequately during and after treatment; ~~and~~ • proximity and availability of clinical trial sites for prospective patients ~~. Utilizing~~ **; and • the impact of any health epidemics, pandemics our or precision medicine approach other contagious outbreaks or geopolitical events** , ~~we~~ **such as war. We** generally focus our development activities on genetically or biomarker defined patients most likely to respond to our therapies. As a result, the potential patient populations for our clinical trials are narrowed, and we may experience difficulties in identifying and enrolling a sufficient number of patients in our clinical trials. **Under** ~~In December 2022, with~~ the **federal** ~~passage of the~~ Food and Drug Omnibus Reform Act, ~~Congress~~ **or FDORA, sponsors are** required ~~sponsors~~ to develop and submit a diversity action plan for each phase 3 clinical trial or any other" pivotal study" of a new drug product. These plans are meant to encourage enrollment of more diverse patient populations in late- stage clinical trials of FDA- regulated products. **In June 2024, as mandated by FDORA, the FDA issued draft guidance outlining the general requirements for diversity action plans. Unlike most guidance documents issued by the FDA, the diversity action plan guidance when finalized will have the force of law.. In January 2025, in response to an executive order issued by President Trump on Diversity, Equity and Inclusion programs, the FDA removed this draft guidance from its website. The implications of this action are not yet known.** If we are not able to adhere to ~~these~~ **any** new requirements, our ability to conduct clinical trials may be delayed or halted. In addition, some of our competitors may have ongoing or planned clinical trials for product candidates that would treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. For example, Rocket Pharma **LTD, or Rocket Pharma,** is developing a gene therapy targeting PK deficiency; Novo Nordisk ~~is developing molecules~~ **A / S,** ~~for~~ **or Novo Nordisk** ~~the treatment of alpha and beta thalassemia~~ , ~~SCD~~ and ~~LR MDS;~~ Pfizer ~~is~~ **Inc., or Pfizer, are** developing molecules for the treatment of SCD; Fulcrum Therapeutics Inc., or Fulcrum, is developing a treatment for SCD; ~~Geron Corporation, or Geron, is developing imetelstat for the treatment of LR MDS (for which they have a Prescription Drug User Fee Act goal date of June 16, 2024 for~~

~~their new drug application); Keros Therapeutics, or Keros, is developing KER- 050 for the treatment of anemia in LR MDS;~~ PTC Therapeutics, Inc., or PTC, and **Otsuka Pharmaceutical Co** ~~Jnana Therapeutics, Inc~~ ., **Ltd** ~~or Jnana, and Homology Medicines Inc~~ ., or ~~Homology~~ **Otsuka** , are developing therapies to treat PKU; and Protagonist Therapeutics, or Protagonist, **with Takeda Pharmaceutical Company Limited, or Takeda,** Ionis Pharmaceuticals, Inc., or Ionis, Silence Therapeutics, or Silence, **Italfarmaco S. p. A., Disc Medicine, Inc., or Disc Medicine,** and Merck **& Co., Inc., or Merck,** are developing therapies to treat PV. Competition for eligible patients may make it particularly difficult for us to enroll a sufficient number of patients to complete our clinical trials for our product candidates in a timely and cost- effective manner. In addition, we have a small number of clinical trial sites for certain clinical trials in the Middle East, including in Lebanon and Israel, that could be affected by the current armed conflict in ~~Israel and~~ the **region** ~~Gaza Strip~~ . We rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials **,** and while we have agreements governing their committed activities, we have limited influence over their actual performance. Our or our collaborators' inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether, or result in increased development costs for our product candidates, which ~~would~~ **could have** ~~cause the value of our company to decline and~~ **an** ~~limit~~ **adverse effect on** our ~~ability to obtain additional~~ **business, results of operations and** ~~financing~~ **financial condition** . Results of preclinical studies and early clinical trials may not be predictive of results of later- stage clinical trials. The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and ~~interim~~ **positive** results of **completed** clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late- stage clinical trials after achieving positive results in earlier stages of development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we ~~,~~ **or** ~~or~~ **our** ~~any~~ collaborators ~~,~~ believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. ~~While we obtained marketing approval~~ **The results of clinical trials** of PYRUKYND ® for the treatment of ~~hemolytic anemia in adults with~~ PK deficiency ~~in the United States~~ and ~~marketing authorization~~ **thalassemia are not predictive** of ~~PYRUKYND ® for the treatment of adults with PK deficiency in the EU and Great Britain, we cannot be certain that we will obtain marketing approval of PYRUKYND ® in other indications. The~~ results of ~~clinical trials of PYRUKYND ® for the treatment of PK deficiency do not predict that PYRUKYND ® will be efficacious in~~ our ongoing clinical trials **of PYRUKYND ®** in other indications, such as ~~thalassemia or~~ SCD **, and the results of our early- stage clinical trials of tebapivat are not predictive of our later stage clinical trial of tebapivat** . If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted. **Interim and preliminary data from clinical trials that we announce or publish from time to time may change as more patient data becomes available and are subject to audit and verification procedures that could result in material changes in the final data. From time to time, we may announce or publish interim or preliminary data from our clinical trials. Interim or preliminary data from clinical trials are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. We also make assumptions, estimations, calculations, and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully evaluate all data. Preliminary or interim data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we have previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could be material and could significantly harm our reputation and business prospects. We conduct clinical trials at sites outside the United States. The FDA may not accept data from trials conducted in such locations, and the conduct of trials outside the United States could subject us to additional delays and expense. We conduct and plan to conduct one or more clinical trials with one or more trial sites that are located outside the United States. The acceptance by the FDA or other regulatory authorities of study data from clinical trials conducted outside their jurisdiction may be subject to certain conditions or may not be accepted at all. In addition, even where the foreign study data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the study is well- designed and well-conducted in accordance with GCP requirements and the FDA is able to validate the data from the study through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA or any comparable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA or any comparable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which could be costly and time- consuming, and may result in current or future product candidates that we may develop not receiving approval for commercialization in the applicable jurisdiction. Conducting clinical trials outside the U. S. also exposes us to additional risks, including risks associated with: • additional foreign regulatory requirements; • foreign exchange fluctuations; •**

compliance with foreign manufacturing, customs, shipment and storage requirements; • cultural differences in medical practice and clinical research; • diminished protection of intellectual property in some countries; and • interruptions or delays in our trials resulting from geopolitical events, such as war or terrorism. We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. We **are** ~~have decided to evolve our approach to exploratory research and drug discovery to prioritize~~ **prioritizing** investment in advancing our late lead- optimization research, while continuing to progress our registration- enabling clinical programs in thalassemia, SCD and pediatric PK deficiency, our phase ~~2a~~ **2** trial in LR MDS, our **phase 1 trial** ~~IND- enabling studies~~ for AG- 181, our PAH stabilizer for the potential treatment of PKU, and **AG- 236,** our **preclinical** development of a **product** ~~licensed siRNA development~~ candidate ~~under our license agreement~~ **for the potential treatment of patients** with ~~Alnylam~~ **PV** . Our resource allocation decisions may cause us to fail to capitalize on viable commercial medicines or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable medicines. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. We or others may later discover that PYRUKYND ®, or any of our product candidates that may receive marketing approval in the future, is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product. It is possible that our clinical trials, or those of any collaborators, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, including PYRUKYND ®, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur: • regulatory authorities may withdraw their approval of the product or seize the product; • we, or any collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials; • additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product; • we may be subject to fines, injunctions or the imposition of civil or criminal penalties; • regulatory authorities may require the addition of **warnings on the product** ~~labeling~~ --- **label** ~~statements~~ ; • we, or any collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients; • we, or any collaborators, could be sued and held liable for harm caused to patients; • the product may become less competitive; and • our reputation may suffer **. For example, in January 2025, the USPI for PYRUKYND ® for the treatment of hemolytic anemia in adults with PK deficiency was updated to include information regarding liver injury observed in patients with thalassemia treated with PYRUKYND ® at a higher dose than recommended for patients with PK deficiency** . PYRUKYND ®, or any of our product candidates that may receive marketing approval in the future, may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success. PYRUKYND ®, or any of our product candidates that may receive marketing approval in the future, may fail to gain and / or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. If PYRUKYND ® or any of our product candidates that may receive marketing approval do not achieve an adequate level of acceptance, we may not generate significant product revenue and ~~we~~ may not become profitable. The degree of market acceptance of PYRUKYND ® and any of our product candidates, if approved for commercial sale, will depend on a number of factors, including: • efficacy and potential advantages compared to alternative treatments **; • the prevalence and severity of any side effects** ; • the ability to offer our medicines for sale at competitive prices; • convenience and ease of administration compared to alternative treatments; • the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; • ensuring uninterrupted product supply; • the strength of **sales,** marketing and distribution support; • sufficient third- party coverage or reimbursement; and • **product labeling or product insert requirements of the FDA or** ~~the~~ **other** ~~prevalence and severity of~~ **regulatory authorities, including** any ~~side effects~~ **limitations or warnings contained in a product' s approved labeling** . If we are unable to maintain sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing PYRUKYND ® or any of our product candidates if they are approved. We have limited experience in the sale, marketing ~~or~~ **and** distribution of pharmaceutical products. To achieve commercial success for approved medicines for which we retain sales and marketing responsibilities, we must either **continue to** develop ~~a~~ **our** sales and marketing organization or outsource these functions to other third parties. We have established sales and marketing capabilities to support our **commercialization** ~~commercial launch~~ of PYRUKYND ® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In addition, in connection with our regulatory approvals in the EU and Great Britain, we are currently providing access to PYRUKYND ® free of charge for eligible patients in those jurisdictions through a global managed access program. We ~~may~~ provide access to PYRUKYND ® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. **Beyond the global managed access program, we continue to evaluate options for the commercialization of PYRUKYND ® outside of the United States, including through exploring potential partnership opportunities, including the NewBridge Agreement.** We may need to further build our sales and marketing infrastructure, either directly or with third- party partners ~~, to maintain our ongoing commercialization efforts and~~ to commercialize PYRUKYND ® in other indications or outside of the United States **,** or to commercialize any of our other product candidates for which we obtain marketing approval. There are risks involved with both

establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive ~~and~~ **,** time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. Factors that may inhibit our efforts to commercialize our medicines on our own include: • our inability to recruit and retain adequate numbers of effective sales and marketing personnel; • the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines; • the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and • unforeseen costs and expenses associated with creating an independent sales and marketing organization. If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability of product revenue to us are likely to be lower than if we were to market and sell any medicines that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing PYRUKYND ® or any of our product candidates for which we obtain marketing approval. We provide certain development estimates related to the development **and regulatory approval** of PYRUKYND ® and our product candidates. If we do not achieve our projected development **or regulatory approval** estimates in the timeframes we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline. From time to time, we provide estimates related to the development of PYRUKYND ® and our product candidates. We also estimate the timing of the anticipated accomplishment of various scientific, preclinical, clinical, regulatory and other product development goals. These estimates may include the commencement or completion of clinical trials ~~and~~ **,** the **timing of completing enrollment, the timing for reporting clinical trial results and the timing of** submission of regulatory filings **in various jurisdictions** . From time to time, we may publicly announce our estimates, including the timing of certain milestones related to our product candidates. All of these estimates are and will be based on numerous assumptions. The actual results and timing of our preclinical ~~and~~ **studies,** clinical trials **and regulatory submissions** can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If our estimates change or we do not meet the timing of our estimates as publicly announced, or at all, the commercialization of our products may be delayed or never achieved and, as a result, our stock price may decline. We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do. We face competition with respect to PYRUKYND ® and **tebapivat and** our ~~current~~ **other** product candidates, and we will face competition with respect to any product candidates that we may seek to develop or commercialize in the future. Potential competitors may include major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the indications for which we are developing our product or our product candidates, such as PK deficiency, thalassemia, SCD, LR MDS, PKU, and PV. For example, Merck and Bristol- Myers Squibb Company, or BMS, are marketing a therapy to treat beta thalassemia and LR MDS **,** and are conducting clinical trials for alpha thalassemia and LR MDS patients that are ~~ESA~~ **erythropoeisis- stimulating agent** naïve and non- transfusion dependent; **Geron Corporation recently announced FDA approval of a treatment for adults with LR MDS with transfusion- dependent anemia;** Novartis International AG, or Novartis, **and** Emmaus Life Sciences ~~, and Pfizer~~ are each marketing therapies to treat SCD ~~, with Pfizer continuing to conduct clinical trials for therapies in SCD~~ ; BioMarin **Pharmaceutical Inc., or BioMarin,** is marketing and conducting clinical trials for therapies to treat PKU; ~~Novo~~ **Pfizer** is conducting clinical trials for **therapies in SCD; Novo Nordisk is conducting clinical trials for** the treatment of alpha and beta thalassemia ~~,~~ **and** SCD ~~and LR MDS~~ ; bluebird is marketing a gene therapy to treat transfusion- dependent beta-thalassemia and SCD; Vertex, with CRISPR, is marketing a gene therapy targeting SCD and transfusion- dependent beta-thalassemia; Fulcrum is conducting clinical trials for a potential treatment for SCD; ~~Geron~~ **PTC** and ~~Keros~~ **Otsuka and** are conducting clinical trials for potential treatments for ~~LR MDS (for which Geron has a Prescription Drug User Fee Act goal date of June 16, 2024 for their new drug application); PTC, Jnana and Homology are conducting clinical trials for potential treatments for~~ PKU; PharmaEssentia Corp, or PharmaEssentia, and Incyte Corporation, or Incyte, are marketing therapies to treat PV, **and Protagonist** with ~~Protagonist~~ **Takeda** , Ionis **, Italfarmaco S. p. A., Disc Medicine, Merck** , and Silence are developing therapies to treat PV **; Rocket Pharma is developing a therapy for the treatment of PK deficiency** ; and a number of other biotechnology companies have product candidates in clinical development in similar indications as ours. There are a variety of treatment options available, including a number of marketed **enzyme replacement therapies, or** ERTs, for treating patients with rare diseases. In addition to currently marketed therapies, there are also a number of products that are either ERTs, gene therapies or PK activators in various stages of clinical development to treat rare diseases. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies or for which there are no approved treatments. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval. ~~There are also a number of product candidates in preclinical or clinical development by third parties to treat rare diseases by targeting similar mechanisms of action or target indications as our product candidates. These companies include large pharmaceutical companies, such as Novartis, Novo Nordisk, Pfizer, BMS, Merck and Vertex as well as biotechnology companies of various sizes, such as BioMarin, bluebird, PTC and Rocket Pharma.~~ Our competitors may

develop products that are more effective, safer, more convenient or less costly than PYRUKYND ® or any product candidates that we are developing or that would render PYRUKYND ® or our product candidates obsolete or non- competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and globally marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and clinical stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These **companies** ~~third parties~~ compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring or in- licensing technologies complementary to, or necessary for, our programs. If the FDA does not grant our products, if and when approved, appropriate periods of ~~data~~ **regulatory** exclusivity before approving generic or follow- on versions of our products, the sales of our products could be adversely affected. With FDA approval of an NDA, the product covered by the application is specified as a " reference- listed drug " in the FDA' s publication, " Approved Drug Products with Therapeutic Equivalence Evaluations, " or the Orange Book. Manufacturers may seek approval of generic versions of reference- listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the sponsor generally must show that its product has the same active ingredient (s), dosage form, strength, route of administration and conditions of use or labeling as the reference- listed drug and that the generic version is bioequivalent to the reference- listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference- listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any reference- listed drug may be ~~typically~~ lost to the generic product. A manufacturer may also submit an NDA under section 505 (b) (2) of the Federal Food, Drug and Cosmetic Act, or FDCA, that references the FDA' s prior approval of the innovator product or preclinical studies and / or clinical trials that were not conducted by, or for, the sponsor and for which the sponsor has not obtained a right of reference. A 505 (b) (2) NDA product, or follow- **on-** product, may be for a new or improved version of the original reference listed drug. The FDA may not approve an ANDA or 505 (b) (2) NDA until any applicable period of **regulatory** ~~non- patent~~ exclusivity for the reference- listed drug has expired. The FDCA provides a period of five years of new chemical entity exclusivity for a new drug containing a new active moiety. Specifically, in cases where such exclusivity has been granted, an ANDA or a 505 (b) (2) NDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference- listed drug is either invalid or will not be infringed by the generic product, in which case the sponsor may submit its application four years following approval of the reference- listed drug. The FDCA also provides a period of three years of new clinical ~~investigation~~ **trial** data exclusivity in connection with the approval of a supplemental indication for the product for which a clinical trial is deemed by the FDA as essential for approval. In the event that a generic or follow- on manufacturer is somehow able to obtain FDA approval without adherence to these periods of ~~data~~ **regulatory** exclusivity, the competition that our approved products may face from generic and follow- on versions could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates. In addition, if there are patents listed for our drug products in the Orange Book, ANDAs and 505 (b) (2) NDAs would be required to include a certification as to each listed patent indicating whether the sponsor intends to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic or follow- on competitor would address such patents, whether we would sue on any such patents or the outcome of any such suit. Product liability lawsuits against us or any collaborators could cause us or our collaborators to incur substantial liabilities and could limit commercialization of any medicines that we or they may develop. We and any collaborators face a risk of product liability exposure related to our product candidates in human clinical trials and face an even greater risk as we or they commercially sell any medicines, including PYRUKYND ®. If we or any collaborators cannot successfully defend ourselves or themselves against claims that our product candidates or medicines caused injuries, we or they could incur substantial costs and liabilities. Regardless of merit or eventual outcome, liability claims may also result in, among other things, decreased demand for any product candidates or medicines that we may develop, reputational harm and lost revenue. Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. Our internal information technology systems, or those of any third parties with which we contract, may fail or suffer security breaches, loss of data or other disruptions which could result in a material disruption of our product development programs, compromise sensitive information related to our business or prevent us from accessing critical information, trigger legal obligations, potentially exposing us to liability, competitive or reputational harm or otherwise adversely affecting our business and financial results. Despite the implementation of security measures, our internal information technology systems and those of third parties with which we contract are vulnerable to damage from computer viruses, worms and other destructive or disruptive software, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third- party vendors ~~and /~~ or business partners, or from cyber incidents by malicious third parties. Cybersecurity incidents are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cybersecurity incidents could include the deployment of harmful malware, ransomware, denial- of- service attacks, unauthorized access to or deletion of files,

social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cybersecurity incidents also could include phishing attempts or e- mail fraud to cause payments or information to be transmitted to an unintended recipient. Attackers may use artificial intelligence and machine learning to launch more automated, targeted and coordinated attacks against targets. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. We may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies. System failures, accidents, cybersecurity incidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed or future trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and our product research, development and commercialization efforts could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events. If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, and, as a result, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain processes, systems and controls designed to prevent these events from occurring, and we have a process to assess, identify and manage threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. We cannot guarantee that the measures we have taken to date, and actions we may take in the future, will be sufficient to prevent any cyber-attacks or security breaches. We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, contractual obligations and failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations. We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally- identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the United States ~~,~~ **and the** EU ~~and United Kingdom~~ . The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, imprisonment of company officials and public censure, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects. There are numerous U. S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to **the federal Health Insurance Portability and Accountability Act of 1996, or** HIPAA **,** establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future. If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. Enforcement activity by the U. S. Department of Health & Human Services, or HHS, can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems. In addition to potential enforcement by HHS, we are also potentially subject to privacy enforcement from the Federal Trade Commission, or FTC. The FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be " unfair " under Section 5 of the FTC Act **of 1914** , as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security that may impact our business. We will need to account for the FTC' s evolving rules and guidance for proper privacy and data security practices in order to mitigate our risk for a potential enforcement action, which may be costly. If we are subject to a potential FTC enforcement action, we may be subject to a settlement order that requires us to adhere to very specific privacy and data security practices, which may impact our business.

We may also be required to pay fines as part of a settlement (depending on the nature of the alleged violations). If we violate any consent order that we reach with the FTC, we may be subject to additional fines and compliance requirements. **A number** ~~States are also active in creating specific rules relating to the processing~~ of ~~personal information. In 2018, California passed into law the California Consumer Privacy Act, or CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt- out of " sales " of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR- like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency — the California Privacy Protection Agency — whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition to California, eleven other~~ states have passed comprehensive privacy laws **, which** ~~similar to the CCPA and CPRA. These laws~~ are either **currently** in effect or will go into effect sometime ~~before~~ **over** the ~~end of 2026~~ **next several years** . ~~Like the CCPA and CPRA, these~~ **These** laws create obligations related to the processing of personal information, as well as special obligations for the processing of " sensitive " data (which includes health data in some cases). Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or are in the process of enacting privacy laws that will go into effect in ~~2024~~ **2025** and beyond ~~, including New Hampshire and New Jersey~~ . Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. ~~For example, Washington state passed a health privacy law that will regulate the collection and sharing of health information, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data, and more states are considering such legislation in 2024.~~ These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products **. Plaintiffs' lawyers in the United States are also increasingly using privacy- related statutes at both the state and federal level to bring lawsuits against companies for their data- related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act. The rise in these types of lawsuits creates potential risk for our business** . Similar to the laws in the United States, there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the **European Economic Area, or** EEA, and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross- border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and / or fines of up to 20 million Euros or up to 4 % of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill. ~~The GDPR places restrictions on the cross- border transfer of personal data from the EU to countries that have not been found by the European Commission to offer adequate data protection legislation, such as the United States. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU- U. S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U. S. The CJEU decision also drew into question the long- term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U. S. This CJEU decision has resulted in increased scrutiny on data transfers generally and may increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners. Additionally, in October 2022, President Biden signed an executive order to implement the EU- U. S. Data Privacy Framework, which would serve as a replacement to the EU- U. S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU- U. S. Data Privacy Framework in December 2022, and the European Commission adopted the adequacy decision on July 10, 2023. The adequacy decision will permit U. S. companies who self- certify to the EU- U. S. Data Privacy Framework to rely on it as a valid data transfer mechanism for data transfers from the EU to the U. S. However, some privacy advocacy groups have already suggested that they will be challenging the EU- U. S. Data Privacy Framework. If these challenges are successful, they may not only impact the EU- U. S. Data Privacy Framework, but also further limit the viability of the standard contractual clauses and other data transfer mechanisms. The uncertainty around this issue has the potential to impact our business internationally. Following Brexit, the UK Data Protection Act 2018 applies to the processing of personal data that takes place in the United Kingdom and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the United Kingdom and the EU have determined, through separate " adequacy " decisions, that data transfers~~

~~between the two jurisdictions are in compliance with the UK Data Protection Act and the GDPR, respectively. The United Kingdom and the U. S. are also in discussions to develop a US- UK " data bridge ", which would function similarly to the EU- U. S. Data Privacy Framework and provide an additional legal mechanism for companies to transfer data from the United Kingdom to the U. S. In addition to the United Kingdom, Switzerland is also in the process of approving an adequacy decision in relation to the Swiss- U. S. Data Privacy Framework (which would function similarly to the EU- U. S. Data Privacy Framework and the U. S.- UK " data bridge " in relation to data transfers from Switzerland to the United States). Any changes or updates to these developments have the potential to impact our business.~~ Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions. While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non- compliant. Similarly, failure to comply with federal and state laws in the United States regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government- imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects. Risks Related to Our Financial Position We face ~~new~~ challenges as a smaller, less diversified company **.** ~~following~~ **Following** the sale of our oncology business to Servier ~~. We developed most of our initial products and product candidates for the treatment of various types of cancer. The sale of our oncology business to Servier~~ in 2021, ~~including our approved products at~~ the ~~time of sale, TIBSOVO ® and IDHIFA ®, has resulted in us being a smaller, less diversified company with a more limited business concentrated on products and product candidates for the treatment of rare diseases. The~~ success of the rare disease business is subject to various risks and uncertainties, including the possibility that we may not be able to successfully commercialize PYRUKYND ®, the possibility **that PYRUKYND ® is not approved for thalassemia or SCD, the possibility** of adverse clinical and other developments in respect of PYRUKYND ® **, tebapivat** or our other product candidates ~~of the rare disease business~~ , and unanticipated changes in applicable laws and regulations that may adversely affect the rare disease business. We may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with rare diseases, than a more diversified company, which could adversely affect our business, financial condition and results of operations. In addition, even with the FDA approval of PYRUKYND ® **for PK deficiency** , the diversification of our revenues, costs and cash flows has diminished following the sale of our oncology business. Our results of operations, cash flows, working capital and financing requirements may be subject to increased volatility and our ability to fund capital expenditures and investments or satisfy other financial commitments may be diminished. Raising additional capital may restrict our operations, require us to relinquish rights to our technologies or product candidates or cause dilution to our stockholders. Until such time, if ever, as we can generate substantial product revenue, including from sales of PYRUKYND ®, we expect to finance our cash needs primarily through cash on hand, ~~a~~ potential ~~milestone~~ **royalty** ~~payment~~ **payments** ~~and royalties from Servier if a new drug application for~~ **with respect to annual U. S. net sales of** vorasidenib **in excess** ~~is approved by the FDA with a label that permits vorasidenib's use as a single agent for the adjuvant treatment~~ of **$** ~~patients with Grade 2 glioma that have an isocitrate dehydrogenase~~ 1 **. 0 billion,** or ~~2 mutation~~ **the Retained Earn- Out Rights** , and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, we may pursue opportunistic debt offerings, and equity or equity- linked offerings. We do not have any committed external source of funds other than the potential ~~milestone~~ **Retained Earn- Out Rights described above** and ~~royalty~~ **we cannot be certain we will ever receive any** payments **as a result of the Retained Earn- Out Rights** ~~that we are eligible to receive with respect to vorasidenib under our purchase agreement with Servier~~ . To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may require us to enter into agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day- to- day activities, which may adversely affect our management' s ability to oversee the development of our product candidates. If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If our existing capital is insufficient to fund our operating expenses and capital expenditures, we will need to raise capital, and if we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts. We expect to incur significant expenses as we continue to advance our ongoing activities. Our estimate as to ~~how long~~ **what extent** we expect our existing cash, cash equivalents, and marketable securities to be available to fund our operating expenses and capital expenditures is based on assumptions that may prove to be

wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds. Our future capital requirements will depend on many factors, including: • the amount and timing of future revenue received from commercial sales of PYRUKYND ® and any of our other product candidates for which we may receive marketing approval; • the amount of ~~contingent consideration~~ **payments, if any,** we ~~ultimately~~ **may** receive ~~from Servier~~ **on account of the Retained Earn- Out Rights** ; • the costs and timing of our ongoing **and future** commercialization activities, including product manufacturing, sales, marketing and distribution, for PYRUKYND ® ~~for the treatment of adults with PK deficiency~~ in the approved jurisdictions **and for any product candidate for which we may receive approval** ~~; • the anticipated cost- savings associated with the evolution of our research organization~~ ; • the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our product candidates; • the costs associated with in- licensing or acquiring assets for pipeline growth, including the amount and timing of future milestone and royalty payments payable to Alnylam pursuant to the license agreement; • the costs, timing and outcome of regulatory review of our product candidates **, including with respect to regulatory submissions for PYRUKYND ® for the treatment of thalassemia** ; • the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property- related claims; • ~~the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval; •~~ our ability to establish and maintain collaborations on favorable terms, if at all; • our ability to successfully execute on our strategic plans; • operational delays due to public health epidemics ~~, including the recent COVID- 19 pandemic~~ ; and • operational delays, disruptions and / or increased costs associated with global economic **and political** developments, rising global energy prices or energy shortages or rationing. We have historically incurred operating losses. We expect to incur losses in the future and may never achieve or maintain profitability. We have a history of incurring operating losses. Our net ~~losses~~ **income** for the **year** ~~twelve months~~ ended December 31, **2024 was $ 673. 7 million and our net loss for the year ended December 31,** 2023 **was** ~~and 2022 were~~ $ 352. 1 million ~~and $ 231. 8 million, respectively~~ . As of December 31, ~~2023~~ **2024** , we had an accumulated deficit of $ ~~822~~ **148** . ~~6~~ **9** million **. The net income we generated in the year ended December 31, 2024 was primarily due to the sale of the Vorasidenib Royalty Rights and our receipt of the Vorasidenib Milestone Payment** . Prior to the sale of our oncology business to Servier in March 2021, we had generated only modest revenue from sales of TIBSOVO ® and, prior to our sale to Royalty Pharma of our royalty rights to IDHIFA ®, from royalties on sales of IDHIFA ®. Following receipt of marketing approval in February 2022, we have begun to commercialize PYRUKYND ® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. **In December 2024, we announced that we submitted an sNDA to the FDA for PYRUKYND ® for the treatment of adult patients with non- transfusion dependent and transfusion- dependent alpha- or beta- thalassemia, which was accepted with standard review by the FDA and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted a MAA to the EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND ® for the treatment of adult patients with non- transfusion dependent and transfusion- dependent alpha- or beta- thalassemia.** We are currently providing access to PYRUKYND ® free of charge for eligible patients in the EU and Great Britain through a global managed access program, and we ~~may~~ provide access to PYRUKYND ® for adult patients with PK deficiency in other jurisdictions through the global managed access program on either a free of charge or for charge basis. **Beyond the global managed access program, we continue to evaluate options for the commercialization of PYRUKYND ® outside of the United States, including through exploring potential partnership opportunities, such as the NewBridge Agreement.** PYRUKYND ® is the first product we have received marketing approval for following the sale of our oncology business. We have neither obtained marketing approval for PYRUKYND ® in any other indications nor have we obtained marketing approval for any of our other product candidates, all of which are in preclinical or clinical development stages. **We** ~~Following the sale of our oncology business, we have financed and~~ expect ~~to continue~~ to finance our operations primarily through cash on hand, **potential** royalty payments ~~from Servier~~ with respect to ~~U. S. net sales of TIBSOVO ® prior to the sale of these~~ -- **the** ~~royalty~~ **Retained Earn- Out** ~~rights~~ **Rights** ~~to Sagard~~ , ~~proceeds from the sale of our rights to the royalty on U. S. net sales of TIBSOVO ® to Sagard, a potential milestone payment and royalties from Servier if a new drug application for vorasidenib is approved by the FDA with a label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2 mutation, the actual and potential future sales of PYRUKYND ®~~ and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, we may pursue opportunistic debt offerings, and equity or equity- linked offerings. We expect to continue to incur significant expenses and net losses until such time as we are able to report profitable results. The net losses we incur may fluctuate significantly from quarter to quarter **and year to year** . We anticipate that we will incur significant expenses if and as we: • **prepare for and** commercially launch PYRUKYND ® for approved indications in approved jurisdictions; • continue to establish and maintain a sales, marketing and distribution infrastructure to commercialize PYRUKYND ® and other product candidates for which we may obtain marketing approval; • initiate and continue clinical trials for our products and product candidates, including PYRUKYND ® in other indications; • continue our research and preclinical development of our product candidates and seek to identify additional product candidates; • seek marketing approvals for our product candidates that successfully complete clinical trials; • require the manufacture of larger quantities of product candidates for clinical development and commercialization; • maintain, expand and protect our intellectual property portfolio; • add additional personnel to support our product research and development and planned future commercialization efforts and our operations; ~~• add equipment and physical infrastructure to support our research and development;~~ and • acquire or in- license other product candidates, medicines and technologies. To become and remain profitable, we must develop and successfully commercialize medicines with significant market potential. This will require us to be successful in a range of challenging

activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post- marketing requirements. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment. ~~The amount of contingent consideration we will receive from the sale of our oncology business to Servier is subject to various risks and uncertainties. Upon closing of the sale of our oncology business to Servier, Servier assumed certain liabilities with respect to the oncology business and paid to us: approximately $ 1. 8 billion in cash, net of certain adjustments for the working capital of the oncology business at the time of closing of the transaction and amounts for a representation and warranty insurance policy. In addition, Servier agreed to pay to us: • $ 200. 0 million in cash if, prior to January 1, 2027, vorasidenib is granted approval for an NDA from the FDA with an approved label that permits vorasidenib' s use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an IDH1 or IDH2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval); • a royalty payment of 5 % of the U. S. net sales (as defined in the purchase agreement with Servier) of TIBSOVO ® from the completion of the transaction through loss of exclusivity of TIBSOVO ®, which we sold to Sagard in October 2022; and • a royalty payment of 15 % of the U. S. net sales (as defined in the purchase agreement with Servier) of vorasidenib from its first commercial sale through loss of exclusivity of vorasidenib. The contingent consideration described above is subject to various risks and uncertainties. Prior to the sale to Sagard, we have received royalties from Servier on U. S. net sales of TIBSOVO ®. We cannot however predict what success, if any, Servier may have in the United States with respect to future sales of vorasidenib, if approved, and, therefore, we cannot predict the amount of royalty payments that we can expect to receive from Servier prior to the loss of exclusivity of vorasidenib. The potential royalty payments with respect to vorasidenib are also subject to deductions and other adjustments under the terms of the purchase agreement, the amounts of which are uncertain as of the date of this report. In addition, there is no guarantee that vorasidenib will be approved by the FDA, and that, as such we will receive the $ 200. 0 million regulatory milestone payment.~~ Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition. Changes in tax law may adversely affect our business or financial condition. **For example** ~~On December 22~~, ~~2017,~~ the **federal** ~~U. S. government enacted the~~ Tax Cuts and Jobs Act **of 2017**, or the Tax Act ~~,~~ ~~which significantly reformed the U. S. Internal Revenue Code of 1986, as amended, or the Code. The Tax Act, among other things, contained significant changes to corporate taxation. As part of Congress' response to the recent COVID- 19 pandemic, economic relief legislation was enacted in 2020~~ and ~~2021. Such legislation contains numerous tax provisions. In addition,~~ the Inflation Reduction Act of 2022, or IRA, **made significant** ~~was signed into law in August 2022. The IRA introduced new tax provisions, including a 1 % excise tax imposed on certain stock repurchases by publicly traded corporations. The 1 % excise tax generally applies to any acquisition by the publicly traded corporation (or certain of its affiliates) of stock of the publicly traded corporation in exchange~~ -- **changes to** ~~for money or other property (other than stock of the corporation~~ **corporate taxation at** ~~itself), subject to a de minimis exception. Thus,~~ the **federal level** ~~excise tax could apply to certain transactions that are not traditional stock repurchases~~. Regulatory guidance under the IRA, the Tax Act, and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen **the** impact of these laws on our business and financial condition. In addition, it is uncertain if and to what extent various states will conform to the IRA, the Tax Act, and additional tax legislation **or whether additional tax legislation could be passed in the future**. Risks Related to Our Dependence on Third Parties We rely and expect to continue to rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing. We do not independently conduct clinical trials of any of our product candidates. We rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. In addition, we currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time. If any of our relationships with these third parties terminate, we may not be able to enter into similar arrangements with alternative third- parties or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. As a result, delays may occur in our product development activities. Although we seek to carefully manage our relationships with our CROs, we could encounter such challenges or delays that could have a material adverse impact on our business, financial condition and prospects. Our reliance on third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our responsibility to comply with any such standards. We and these third parties are required to comply with current good clinical practices, or cGCP, which are regulations and guidelines enforced by the FDA, the ~~Competent~~ **competent** ~~Authorities~~ **authorities** of the ~~Member~~ **member** ~~States~~ **states** of the EEA and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA, or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you a given regulatory authority will determine that any of our clinical trials comply with cGCP regulations. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a U. S. government- sponsored database, clinicaltrials. gov, within certain timeframes. Failure to do so can result in fines,

adverse publicity, and civil and criminal sanctions. We are exposed to risk of fraud or other misconduct by such third parties. Furthermore, third parties on whom we rely may also have relationships with other entities, some of which may be our competitors. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ~~on- going~~ **ongoing** clinical, nonclinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, **or** if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to successfully commercialize our medicines. If either we or any third parties on which we rely are adversely impacted by **geopolitical events,** rising global energy costs or energy shortages or rationing, delays may occur in our product development activities, which delays could have a material adverse impact on our business, financial condition and prospects. We also rely and expect to continue to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our medicines, producing additional losses and depriving us of potential product revenue. We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and for commercialization. We do not have any manufacturing or supply chain **-** related facilities. We currently rely, and expect to continue to rely, on third- party manufacturers for the materials and manufacture of our product candidates for preclinical and clinical testing and for commercial supply of PYRUKYND ® and any product candidate for which we obtain marketing approval. Although we have entered into long- term supply agreements for commercial supply of PYRUKYND ® with third- party manufacturers, we may be unable to establish similar long- term supply agreements with third- party manufacturers with respect to our other product candidates or to do so on acceptable terms. Even if we are able to establish agreements with third- party manufacturers, reliance on third- party manufacturers entails additional risks, including: • reliance on the third party for regulatory compliance, quality assurance, environmental and safety and pharmacovigilance reporting; • the possible breach of the manufacturing agreement by the third party; and • the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us. Third- party manufacturers may not be able to comply with cGMPs, regulations or similar regulatory requirements on a global basis. Our failure, or the failure of our third- party manufacturers, to comply with currently applicable regulations, or regulations or specifications to which we become subject in the future, could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations. **In addition, we currently rely on foreign third- party manufacturers and / or CROs, including those in China, and will likely continue to rely on foreign third- party manufacturers and / or CROs in the future. Foreign third- party manufacturers and / or CROs may be subject to U. S. legislation, including sanctions, trade restrictions and other foreign regulatory requirements which could increase the cost or reduce the supply of material or services available to us, delay the procurement or supply of such material or services, or have an adverse effect on our ability to secure significant commitments from governments to purchase our potential therapies. Moreover, in September 2024, the U. S. House of Representatives passed the BIOSECURE Act (H. R. 7085) and the Senate has advanced a substantially similar bill (S. 3558), which legislation, if passed and enacted into law, would restrict the ability of U. S. biopharmaceutical companies like us to purchase services or products from, or otherwise collaborate with, specifically named Chinese biotechnology companies and authorizes the U. S. government to impose such restrictions on entities transaction with additional Chinese biotechnology companies as a condition of U. S. government contract, grant, and loan funding. The legislation contains a grandfathering provision that would prevent disruption to the provision of services or products furnished under contracts with the targeted biotechnology companies entered before the effective date of the legislation until January 1, 2032. It is possible some of our contractual counterparties could be impacted by this legislation.** If either we or any third parties on which we rely are adversely impacted by restrictions resulting from the ~~recent COVID- 19 pandemic, the~~ emergence of ~~another~~ public health ~~epidemic~~ **epidemics** , by rising global energy costs or energy shortages or rationing and / or **geopolitical events and** the impacts of the Russia- Ukraine war, our supply chain may be disrupted, limiting our ability to manufacture our product candidates for our clinical trials and research and development operations and our product for commercialization. Any performance failure on the part of our existing or future manufacturers could delay preclinical development, clinical development, marketing approval or our commercialization efforts. Due to the volatility of the supply networks globally, we have obtained regulatory approval for redundant supply of raw materials and active pharmaceutical ingredient for PYRUKYND ®, and have an ongoing program to monitor supply, including establishing safety stocks. While we maintain a broad safety stock of drug product, we do not currently have arrangements in place for redundant supply for drug product. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product or our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement. Our current and anticipated future dependence upon others for the manufacture of our product candidates or medicines may adversely affect our future profit margins and our ability to commercialize any medicines that receive marketing approval on a timely and competitive basis. We may depend on collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates. We may seek collaborations for the development and commercialization of our product candidates **, such as the NewBridge Agreement,** with large and mid- size pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators. Collaborations are complex and time- consuming to negotiate and document. Whether we reach a definitive agreement for a collaboration will

depend, among other things, upon our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator' s evaluation of a number of factors. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. Collaborators may have rights that restrict us from entering into future agreements on certain terms with potential collaborators. If we enter into any such arrangements with collaborators, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator' s strategic focus or available funding **,** or external factors such as an acquisition that diverts resources or creates competing priorities. Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing, which may result in a need for additional capital to pursue further development or commercialization of the applicable product candidate. Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation. Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our medicines or product candidates or that result in costly litigation or arbitration that diverts management attention and resources. In addition, our ability to enter into arrangements with collaborators in specific regions, such as the Middle East, may be affected by localized geopolitical unrest or military conflict, such as the current armed conflict in ~~Israel and~~ the **region** ~~Gaza Strip~~ . Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. Risks Related to Our Intellectual Property If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected. Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary medicines and technology. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and medicines that are important to our business. We do not yet have issued patents for all our most advanced product candidates in all markets in which we intend to commercialize but we continue to actively pursue patent protection for our assets around the world. The patent prosecution process is costly and time- consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify and / or file patent applications on every aspect of our research and development output that is or may be eligible for patent protection. Although we enter into non- disclosure and confidentiality agreements with parties who may have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, **CROs** ~~contract research organizations~~ , contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. There is also the possibility that loss or theft of data or records may jeopardize the ability to seek patent protection or impede the progress or drafting of patent applications. We have licensed patent rights, and in the future may license additional patent rights, from third parties. Such licenses may be accompanied by milestone and / or royalty payment obligations. These licensed patent rights may be valuable to our business, and we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or medicines underlying such licenses. We cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. If any such licensors fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties also apply to patent rights we own. The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or medicines or that effectively prevent others from commercializing competitive technologies and medicines. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. **The** ~~Assuming the other requirements for patentability are met, prior to March 2013, in the~~ United States **maintains** ~~, the first to make the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. Beginning in March 2013, the United States transitioned to~~ a first inventor to file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent. We may be subject to a third- party pre- issuance submission of prior art to the U. S. Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, post- grant and inter partes review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our

inability to manufacture or commercialize medicines without infringing third- party patent rights. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non- infringing manner. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of the patent or in one or more patent claims being narrowed or invalidated, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and medicines. Given the significant amount of time required for the discovery, development, preclinical and clinical testing and regulatory review and approval of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. In such circumstances we would be relying primarily on regulatory or marketing exclusivity to exclude others from commercializing a generic version of our products. We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful. Competitors may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. Third parties may initiate legal proceedings alleging that we or our collaborators are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product and product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. We have in the past **, are** and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our medicines and technology, including opposition, derivation, revocation, reexamination, post- grant and inter partes review or interference proceedings before the USPTO or other patent offices around the world. ~~We are not aware~~ **For example, two** of ~~any legal~~ **the European patents in our mitapivat portfolio, neither being the primary compound patent, have been challenged in opposition** proceedings ~~having been filed against us following~~ **in the European Patent Office. The revocation of either of** ~~the~~ **these** ~~sale of our oncology business~~ **European patents could potentially allow additional competitor drugs, if approved,** to ~~Servier~~ **enter the European marketplace earlier than anticipated** . Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we or one of our collaborators are found to infringe a third party' s intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our medicines and technology. However, we or our collaborators may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborators were able to obtain a license, it could be non- exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us. We or our collaborators could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, we or our collaborators could be found liable for monetary damages. A finding of infringement could prevent us or our collaborators from commercializing our product and product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we or our collaborators have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers. Many of our employees, consultants or advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual' s current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our organization. Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities. 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. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our

ability to compete in the marketplace. If we are unable to protect the confidentiality of our confidential information related to our proprietary platforms and technology, our business and competitive position could be harmed. In addition to seeking patents for some of our technology and medicines, we also rely on maintaining the confidentiality of unpatented know- how, technology and other proprietary information, to maintain our competitive position. For example, we consider the confidential information and know- how related to our cellular metabolism technology platform to be our primary intellectual property assets in this space. Unpatented proprietary technical information and know- how can be difficult to protect. We seek to protect this proprietary technical information and know- how, in part, by entering into non- disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, **CROs** ~~contract research organizations~~ , contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated proprietary information is difficult, expensive and time- consuming, and the outcome is unpredictable. If any of our proprietary technical information and know- how were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. Moreover, we anticipate that with respect to this platform, at least some of this technical information and know- how will, over time, be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions. Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters Even if we complete necessary preclinical studies and clinical trials, the marketing approval process is expensive, time- consuming and uncertain **,** and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired. Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or our collaborators ultimately obtain may be limited or subject to restrictions or post- approval commitments that render the approved medicine not commercially viable. The FDA, EMA and other foreign regulatory authorities have substantial discretion in the approval process. Accordingly, it is possible that the FDA or EMA may refuse to accept for substantive review any NDA, **supplemental** ~~sNDA~~ - **NDA** or MAA that we submit for our product candidates, or may conclude after review of our data that our marketing application is insufficient to obtain marketing approval of our product candidates. If the FDA or EMA does not accept or approve our applications for any of our product candidates, the applicable regulator may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before reconsidering our applications. Depending on the extent of these or any other FDA- or EMA- required trials or studies, approval of any marketing applications that we submit may be delayed by several years, or may require us to expend more resources than we planned. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA or EMA to approve any marketing applications. We may not be successful in obtaining FDA or EMA approval of our product candidates on a timely basis, or ever. We have limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third- party **CROs** ~~contract research organizations~~ to assist us in this process, and failure to obtain marketing approval for our product candidates will prevent us from commercializing the product candidate in the applicable jurisdictions **. Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or a comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates** . Further, the process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Disruptions at the FDA and other agencies may prolong the time necessary for regulatory submissions to be reviewed and / or new drugs to be approved by necessary government agencies, which would adversely affect

our business. For example, over the last several years, the U. S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown were to occur, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. For example, should the FDA determine that an inspection is necessary for approval of a regulatory submission and an inspection cannot be completed during the review cycle, and the FDA does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue a complete response letter or defer action on the regulatory submission until an inspection can be completed. ~~Finally~~ **In addition, we could be adversely affected by several significant administrative law cases decided by the U. S. Supreme Court in 2024, including most notably, Loper Bright Enterprises v. Raimondo, which overruled the Supreme Court' s previous ruling that courts defer to reasonable agency interpretations of statutes that are silent or ambiguous on a particular topic. The ruling requires courts to exercise their independent judgment when deciding whether an agency has acted within its statutory authority, and that courts may not defer to an agency interpretation solely because a statute is ambiguous. This decision and other administrative law cases may result in additional legal challenges to regulations and guidance issued by federal regulatory agencies, including the FDA and CMS, that we have relied on and intend to rely on in the future. Any such challenges, if successful, could have a material impact on our business. In addition to potential changes to regulations and agency guidance as a result of legal challenges, these decisions may result in increased regulatory uncertainty and delays in and other impacts to the agency rulemaking process, any of which could adversely impact our business and operations. Additionally** , our ability to develop and market new drug products may be ~~threatened by the results of ongoing~~ **impacted based on current or future** litigation **in the federal court system** challenging the FDA' s approval of ~~another~~ -- **other** ~~company~~ **companies ' '** ~~s drug~~ **drugs** . ~~Specifically, in April 2023, the U. S. District Court for the Northern District of Texas invalidated the approval by the FDA of mifepristone, a drug product which was originally approved in 2000 and whose distribution is governed by various measures adopted under a REMS. In reaching that decision, the district court made a number of findings that may negatively impact the development, approval and distribution of new drug products in the United States. The Court of Appeals for the Fifth Circuit declined to order the removal of mifepristone from the market, finding that a challenge to the FDA' s initial approval in 2000 is barred by the statute of limitations. But the Court of Appeals for the Fifth Circuit did hold that plaintiffs were likely to prevail in their claim that changes allowing for expanded access of mifepristone that the FDA authorized in 2016 and 2021 were arbitrary and capricious. In December 2023, the Supreme Court announced that it will review the appeals court decision~~ . Depending on the outcome of this **type of** litigation ~~and the regulatory uncertainty it has engendered~~ , our ability to develop new drug product candidates and to maintain approval of existing drug products **could be** ~~and measures adopted under a REMS is~~ at risk and our efforts to develop and market new drug products could be delayed, undermined or subject to protracted litigation **. Finally, with the change in presidential administrations in 2025, there is substantial uncertainty as to how, if at all, the new administration will seek to modify or revise the requirements and policies of the FDA and other regulatory agencies with jurisdiction over our product candidates. The impending uncertainty could present new challenges or potential opportunities as we navigate the clinical development and approval process for our product candidates** . If we or our collaborators experience delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenue will be materially impaired. Failure to obtain marketing approval in foreign jurisdictions would prevent our medicines from being marketed in such jurisdictions and any of our medicines that are approved for marketing in such jurisdiction will be subject to risk associated with foreign operations. In order to market and sell our medicines in the EU and many other foreign jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Moreover, approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Although we have received marketing authorization for PYRUKYND ® for the treatment of adults with PK deficiency in the EU and Great Britain, we may not be able to file for additional marketing approvals and may not receive necessary approvals to commercialize our medicines in any other foreign market. ~~Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the withdrawal of the United Kingdom from the EU on December 31, 2020, commonly referred to as Brexit. Since the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, the consequences of Brexit and the impact on the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom remains unclear. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to EU rules under the Northern Ireland Protocol. The United Kingdom and the EU have however agreed to the Windsor Framework which fundamentally changes the existing system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the United Kingdom. Once implemented, the changes introduced by the Windsor Framework will result in the MHRA being responsible for approving all medicinal products destined for the United Kingdom market (Great Britain and Northern Ireland), and the EMA will no longer have any role in approving~~

~~medicinal products destined for Northern Ireland. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may prevent us from commercializing any product candidates in the United Kingdom and / or the EU and may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom, which could significantly and materially harm our business.~~ In addition, foreign regulatory authorities may change their approval policies and new regulations may be enacted. For instance, **EU** ~~the European Union~~ pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative ~~, launched by the European Commission in November 2020~~ . The European Commission' s proposal for revision of several legislative instruments related to medicinal products (including potentially reducing the duration of regulatory data protection and revising the eligibility for expedited pathways) was published ~~on~~ **in** April ~~26,~~ 2023 **, and the European Parliament has requested several amendments in April 2024** . The proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may **,** however **,** have a significant impact on the pharmaceutical industry and our business in the long term. We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States. In addition, we do not have experience commercializing products outside of the United States and such efforts may depend on our ability to find a suitable collaborator. Fast track designation and / or priority review designation by the FDA or PRIME designation in the EU may not actually lead to a faster development or regulatory review or approval process, nor does it assure approval of the product candidate by the FDA or the EMA. We may seek fast track designation, priority review designation and / or PRIME designation for our product candidates. If a product candidate is intended for the treatment of a serious or life- threatening disease or condition and the product candidate demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA fast track designation. Further, if the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. Receiving priority review from the FDA does not guarantee approval within the six- month review cycle or thereafter. The FDA has broad discretion on whether to grant fast track designation and / or priority review designation to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Even if our product candidates receive fast track designation and / or priority review designation, we may not experience a faster development process, review or approval, if at all, compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. In addition, in the EU, the PRIME designation program focuses on product candidates that target conditions for which there exists no satisfactory method of treatment in the EU or product candidates that may offer a major therapeutic advantage over existing treatments. The benefits of a PRIME designation include, among other things, the potential to qualify product for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME designation enables a sponsor to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if our product candidates receive PRIME designation, we may not experience a faster development process, review or approval compared to conventional EMA procedures and it does not assure or increase the likelihood of the EMA' s grant of a marketing authorization. We, or any collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for our drug candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing drugs. Regulatory authorities in some jurisdictions, including the United States and ~~Europe~~ **the E. U.** , may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200, 000 individuals annually in the United States. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same product for that time period. The applicable period is seven years in the United States and **currently** ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Moreover, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. ~~In addition, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.~~ The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies ~~. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term " same disease or condition " means the designated " rare disease or condition " and could not be interpreted by the FDA to mean the " indication or use. " Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond~~

~~the scope of that court order, the FDA will continue to apply its existing regulations tying orphan- drug exclusivity to the uses or indications for which the orphan drug was approved~~ . We do not know if, when, or how the FDA or Congress may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted. Any product or product candidate for which we or our collaborators obtain marketing approval could be subject to restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our medicines, when and if any of them are approved. Any product or product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post- approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and record keeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post- marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a **REMS** ~~risk evaluation and mitigation strategy~~ . The FDA and other agencies, including the **Department of Justice, or** DOJ, closely regulate and monitor the post- approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off- label use and if we market our medicines for uses other than their respective approved indications, we may be subject to enforcement actions for off- label marketing. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws, which violations may result in the imposition of significant administrative, civil and criminal penalties. Our relationships with healthcare providers, physicians and third- party payors are subject to applicable anti- kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Healthcare providers, physicians and third- party payors will play a primary role in the recommendation and prescription of PYRUKYND ® and any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third- party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute PYRUKYND ® and any other medicines for which we obtain marketing approval. **Such** ~~Restrictions under applicable federal and state healthcare~~ laws and regulations include ~~the following: • the~~ federal Anti-Kickback ~~Statute~~ **Statue** ~~prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid~~ ; • the federal False Claims Act ~~imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per- claim penalties~~ ; ~~• the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;~~ • HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ~~and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information~~ ; • the federal Physician Payments Sunshine Act ~~requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals and other covered recipients~~ ; and • analogous state and foreign laws and regulations ~~, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers~~ . Some state laws require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. The provision of benefits or advantages to physicians to induce or encourage the

prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. The provision of benefits or advantages to physicians is governed by the national anti- bribery laws of **member states of the EU, or the** EU Member States, such as the U. K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician' s employer, his or her competent professional organization and / or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment. PYRUKYND ® or any product candidate that we commercialize may become subject to unfavorable pricing regulations and third- party reimbursement practices, which would harm our business. We ~~have~~ built our commercial infrastructure to support the **commercialization** ~~commercial launch~~ of PYRUKYND ® in adult PK deficiency **in the United States, and have expanded this infrastructure to support the potential commercial launch of PYRUKYND ® in thalassemia** in the United States. We are providing access to PYRUKYND ® free of charge for eligible patients in the EU and Great Britain through a global managed access program, and we ~~may~~ provide access to PYRUKYND ® for adult patients with PK deficiency in other jurisdictions through the global managed access program on either a free of charge or for charge basis. The commercial success of PYRUKYND ® or of any of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third- party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement is not available, or reimbursement is available only to limited levels, we, or any collaborators, may not be able to successfully commercialize PYRUKYND ® or our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third- party payors **,** and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time- consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. There is significant uncertainty related to third- party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired. As a result, we, or any collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval. Patients who are provided medical treatment for their conditions generally rely on third- party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any collaborators, to commercialize PYRUKYND ® or any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third- party payors. Third- party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third- party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any collaborators to sell PYRUKYND ® or our product candidates profitably. These payors may not view our products, if any, as cost- effective, and coverage and reimbursement may not be available to our customers, or those of any collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost- control initiatives could cause us, or any collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenue. If the prices for our products, if any, decrease or if governmental and other third- party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer. In addition, increasingly, third- party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for PYRUKYND ® or any product candidate that we, or any collaborator, may commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government- funded and private payors for PYRUKYND ® or any of our product candidates for which we, or any collaborator, may obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition. Current and future healthcare reform legislation may increase the difficulty and cost for us and any collaborators to obtain reimbursement and commercialize our drug candidates. In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post- approval activities and

affect our ability, or the ability of any collaborators, to profitably sell PYRUKYND ® or any other product **candidate** for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the ACA. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. This legislation resulted in aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year, which will remain in effect for six months into fiscal year 2032. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4 %. The Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Consolidated Appropriations Act delays the 4 % Statutory Pay- As- You- Go Act of 2010 ~~, or PAYGO,~~ sequester for two years, through the end of calendar year 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4 % cut to the Medicare program would have taken effect in January 2023. The Consolidated Appropriations Act' s health care offset title includes Section 4163, which extends the 2 % Budget Control Act of 2011 Medicare sequester for six months into fiscal year 2032 and lowers the payment reduction percentages in fiscal years 2030 and 2031. Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, in 2017, Congress repealed the " individual mandate. " The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On November 10, 2020, the Supreme Court heard oral arguments as to whether the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On ~~February 10, 2021, the Biden Administration withdrew the federal government' s support for overturning the ACA. On~~ June 17, 2021, the Supreme Court struck down the lower court rulings, finding that the plaintiffs did not have standing to challenge the ACA' s minimum essential coverage provision at issue in the case. The ~~Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked these Orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. This Executive Order also directs the U. S. Department of Health and Human Services to create a special enrollment period for the Health Insurance Marketplace in response to the recent COVID- 19 pandemic. We cannot predict how federal agencies will respond to such Executive Orders. The~~ prices of prescription pharmaceuticals in the United States and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our drug products, if and when approved, and / or the sustainability of those prices. The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. ~~To date, there have been several recent U. S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and Medicaid. To those ends, President Trump issued several executive orders intended to lower the costs of prescription products. Certain provisions of these orders have been reflected in promulgated regulations, including an interim final rule implementing a most favored nation model for prices, which would tie Medicare Part B payments for certain physician- administered pharmaceuticals to the lowest price paid in other economically advanced countries. Such final rule has been subject to a nationwide preliminary injunction, and, on December 29, 2021, Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With the issuance of this rule, CMS stated it will explore all options to incorporate value into payments for Medicare Part B drugs and improve beneficiaries' access to evidence- based care. In addition, in October 2020, the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. That regulation was challenged in a lawsuit by the Pharmaceutical Research and Manufacturers of America, or PhRMA, but the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue HHS. Nine states (Colorado, Florida, Maine, New Hampshire, New Mexico, North Dakota, Texas, Vermont and Wisconsin) have passed laws allowing for the importation of drugs from Canada. Certain of these states have submitted Section 804 Importation Program proposals and are awaiting FDA approval. On January 5, 2023, the FDA approved Florida' s plan for Canadian drug importation. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point- of- sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the IRA, has been delayed by Congress to January 1, 2032. The IRA has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA~~

~~requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single- source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high- cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Medicare Part D drugs in 2027, 15 Medicare Part B or Part D drugs in 2028, and 20 Medicare Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated " maximum fair price " under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out- of- pocket drug costs at an estimated $ 4, 000 a year in 2024 and, thereafter beginning in 2025, at $ 2, 000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or " catastrophic period " of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100 % of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co- insurance and co- payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out- of- pocket expenses, each of which could have potential pricing and reporting implications. In June 2023, Merck filed a lawsuit against the HHS and CMS asserting that, among other things, the IRA' s Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U. S. Chamber of Commerce and pharmaceutical companies, also filed lawsuits in various courts with similar constitutional claims against HHS and CMS.~~ We ~~expect that litigation involving these and other provisions of the IRA will continue, with unpredictable and uncertain results. Accordingly, while it is currently unclear how the IRA will be effectuated, we~~ cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition. At the state level, individual states are increasingly aggressive in passing legislation and implementing 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. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product or product candidates or additional pricing pressures. In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the United States and the EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost- effectiveness of our product to other available therapies. If reimbursement of our product is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed. We are subject to U. S. and foreign export control, import, sanctions, anti- corruption and anti- money laundering laws with respect to our operations , and non- compliance with such laws can subject us to criminal and / or civil liability and harm our business. We are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Control, the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, and other state and national anti- bribery and anti- money laundering laws in countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, third- party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government- affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and / or to obtain necessary permits, licenses, and other

regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third- party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities. Noncompliance with such laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and / or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management' s attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens. With the passage of the CREATES Act, we are exposed to possible litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market- based terms for testing in support of their ANDAs and 505 (b) (2) applications. ~~In December~~ **Under the Creating and Restoring Equal Access to Equivalent Samples Act of** 2019, **or** ~~former President Trump signed legislation intended to facilitate the development of generic and biosimilar products. The bill, previously known as~~ the CREATES Act, authorizes sponsors of ANDAs and 505 (b) (2) applications to file lawsuits against companies holding NDAs that decline to provide sufficient quantities of an approved reference drug on commercially reasonable, market- based terms. Drug products on FDA' s drug shortage list are exempt from these new provisions unless the product has been on the list for more than six continuous months or the FDA determines that the supply of the product will help alleviate or prevent a shortage. For the purposes of the statute, the term " commercially reasonable, market- based terms " is defined as (1) the nondiscriminatory price at or below the most recent wholesale acquisition cost for the product, (2) a delivery schedule that meets the statutorily defined timetable, and (3) no additional conditions on the sale. To bring an action under the statute, an ANDA or 505 (b) (2) sponsor must take certain steps to request the reference product, which, in the case of products covered by a **REMS** ~~Risk Evaluation and Mitigation Strategy~~ with elements to assure safe use, include obtaining authorization from the FDA for the acquisition of the reference product. If the sponsor does bring an action for failure to provide a reference product, there are certain affirmative defenses available to the NDA holder, which must be shown by a preponderance of evidence. If the sponsor prevails in litigation, it is entitled to a court order directing the NDA holder to provide, without delay, sufficient quantities of the applicable product on commercially reasonable, market- based terms, plus reasonable attorney fees and costs. Additionally, the statutory provisions authorize a federal court to award the product developer an amount " sufficient to deter " the NDA holder from refusing to provide sufficient product quantities on commercially reasonable, market- based terms if the court finds, by a preponderance of the evidence, that the NDA holder did not have a legitimate business justification to delay providing the product or failed to comply with the court' s order. Although we intend to **fully** comply ~~fully~~ with the terms of these new statutory provisions, we are still exposed to potential litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market- based terms for testing in support of ANDAs and 505 (b) (2) applications. Such litigation would subject us to additional costs, damages and reputational harm, which could lead to lower revenues. The CREATES Act may enable generic competition with PYRUKYND ® and any of our product candidates, if approved, which could impact our ability to maximize product revenue. If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business. We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. Risks Related to Employee Matters and Managing Growth Our future success depends on our ability to retain our key executives and scientific leadership and to attract, retain and motivate qualified personnel. We are highly dependent on the principal members of our management and scientific teams, each of whom is employed " at will, " meaning we or they may terminate the employment relationship at any time. We do not maintain " key person " insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives. We cannot predict the likelihood, timing or effect of future transitions among our executive leadership. Recruiting and retaining qualified scientific, clinical, manufacturing, regulatory and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and universities and research institutions for similar personnel. Our consultants and advisors ~~, including our scientific co- founders,~~ who assist us in formulating our research and development and commercialization strategy

may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Furthermore, ~~the recent COVID- 19 pandemic and~~ our flexible workplace policy ~~allowing~~ **which allows** employees to work from home may make it difficult for us to maintain our corporate culture. In the future we may experience growth in the number of our development, regulatory and sales and marketing personnel. To manage any anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Any inability to manage growth could delay the execution of our business plans or disrupt our operations. Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business. We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations or regulations in other jurisdictions, provide accurate information to the FDA or other regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately, disclose unauthorized activities to us, or comply with securities laws. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, including for illegal insider trading activities, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions. Risks Related to Our Common Stock and Other Matters Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management. Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our Board of Directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our Board of Directors. Among other things, these provisions: • establish a classified board of directors such that not all members of the board are elected at one time; • allow the authorized number of our directors to be changed only by resolution of our Board of Directors; • limit the manner in which stockholders can remove directors from our Board of Directors; • establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our Board of Directors; • require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent; • limit who may call stockholder meetings; • authorize our Board of Directors to issue preferred stock without stockholder approval, which could be used to institute a shareholder rights plan, or so- called " poison pill, " that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our Board of Directors; and • require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. The price of our common stock is likely to be volatile, which could result in substantial losses for purchasers of our common stock. The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, since January 1, 2015 the closing price of our common stock on the Nasdaq Global Select Market has ranged from $ 17. 06 per share to $ 135. 01 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. While the full extent of the economic impact of the recent ~~COVID- 19 pandemic or recent~~ increases in inflation rates (particularly as it relates to clinical- or manufacturing- related costs) may be difficult to assess or predict, such impacts have already caused, and are likely to result in further, significant disruption of global financial markets, which may reduce our ability to access capital either at all or on favorable terms. If we are unable to raise additional funds through equity or debt financings when needed or on attractive terms, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. The market price for our common stock may be influenced by many factors, including: • our success in launching and commercializing PYRUKYND ® ~~; • the decision to focus our efforts on our rare disease business following the sale of our oncology business to Servier; • the evolution of our research organization~~ ; • announcements by us or our competitors of significant acquisitions, in- licensing arrangements, strategic partnerships, joint ventures, collaborations or capital commitments; • the timing and results of clinical trials of product candidates, or our competitors' product candidates; • regulatory actions with respect to our product or product candidates or our competitors' products and product candidates; • commencement or termination of collaborations for our development programs; • failure or discontinuation of any of our development programs; • regulatory or legal developments in the United States and other countries; • developments or disputes concerning patent applications, issued patents or other proprietary rights; • the recruitment or departure of key personnel; • the

level of expenses related to any of our products, product candidates or development programs; • the results of our efforts to develop additional product candidates and products; • actual or anticipated changes in estimates as to financial results or development timelines; • announcement or expectation of additional financing efforts; • sales of our common stock by us, our insiders or other stockholders ~~, including shares issuable upon exercise of outstanding stock options and upon vesting of stock units under our stock incentive plans~~ ; • variations in our financial results or results of companies that are perceived to be similar to us; • changes in estimates, evaluations or recommendations by securities analysts, that cover our stock or the failure by one or more securities analysts to continue to cover our stock; • changes in the structure of healthcare payment systems; • the societal and economic impact of public health epidemics or pandemics, ~~such as the recent COVID- 19 pandemic~~ and any recession, depression or sustained market event resulting from such epidemics or pandemics; • market conditions in the pharmaceutical and biotechnology sectors; • general economic, industry and market conditions; and • the other factors described in this " Risk Factors " section. In the past, following periods of volatility in the market price of a company' s securities, securities class- action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert managements' attention and resources, which could seriously harm our business, financial condition, results of operations and prospects. We also cannot guarantee that an active trading market for our shares will be sustained. An inactive trading market for our common stock may impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration. Our financial condition and operating results also may fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance. Our executive officers, directors and principal stockholders maintain the ability to significantly influence all matters submitted to stockholders for approval. As of December 31, ~~2023~~ **2024** , our executive officers, directors and principal stockholders, in the aggregate, beneficially owned shares representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire. Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited. Under Section 382 **and 383** of the Code and corresponding provisions of state law, if a company undergoes an " ownership change, " generally defined as a greater than 50 % change (by value) in its equity ownership by certain stockholders over a three- year period, the company' s ability to use its pre- change net operating loss carryforwards and other pre- change tax attributes (such as research tax credits) to offset its post- change taxable income may be limited. Our prior equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. We completed a review of our changes in ownership through December 31, ~~2023~~ **2024** , and determined that we did not have a qualified ownership change since our last review as of December 31, ~~2022~~ **2023** . Future ownership changes under Section 382 may limit the amount of net operating loss and tax credit carryforwards that we could potentially utilize to reduce future tax liabilities. There is also a risk that due to regulatory changes, such as suspensions on the use of net operating losses, or other unforeseen reasons, our existing net operating losses could expire or otherwise become unavailable to offset future income tax liabilities. The Tax Act, as amended by the Coronavirus Aid, Relief, and Economic Security Act includes changes to U. S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. In addition, state net operating losses generated in one state cannot be used to offset income generated in another state. For these reasons we may be unable to use a material portion of our net operating losses and other tax attributes. Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts. We are subject to taxation in numerous U. S. states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different from previous periods or our current expectations due to numerous factors, including as a result of changes in the mix of our profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors may result in tax obligations in excess of amounts accrued in our financial statements. We incur costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices. We have incurred and will continue to incur significant legal, accounting and other expenses as a public company. The Sarbanes- Oxley Act of 2002, the Dodd- Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations. Our management and other personnel devote, and will need to continue to devote, a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be the sole source of gain for our stockholders. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future. ~~64~~