Risk Factors Comparison 2024-03-05 to 2023-02-07 Form: 10-K

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Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this Annual Report on Form 10- K, including our consolidated financial statements and the related notes appearing elsewhere in this Annual Report on Form 10- K and in our other filings with the Securities and Exchange Commission, or SEC, before deciding to invest in our common stock. The risks described below are not the only risks facing our company. The occurrence of any of the following risks, or of additional risks and uncertainties not presently known to us or that we currently believe to be immaterial, could cause our business, prospects, operating results and financial condition to suffer materially. In such event, the trading price of our common stock could decline, and you might lose all or part of your investment. Risks Related to Our Financial Position and Need for Additional Capital Risks Related to Past Financial Condition We are a clinical- stage biopharmaceutical company and we have incurred significant losses since our inception. We anticipate that we will continue to incur significant losses for the foreseeable future. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate effect or an acceptable safety profile, gain regulatory approval and become commercially viable. We have no products approved for commercial sale and have not generated any revenue to date, and we will continue to incur significant research and development and other expenses related to our clinical development and ongoing operations. As a result, we are not profitable and have incurred losses in each period since our inception. Since our inception, we have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical trials. Our financial condition and operating results, including net losses, may fluctuate significantly from quarter to quarter and year to year. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance. Additionally, net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. Our net losses were $ **123. 3 million and $** 214. 0 ~~million and $ 167. 1~~ million for the years ended December 31, **2023 and** 2022 ~~and 2021~~, respectively. As of December 31, ~~2022~~ **2023**, we had an accumulated deficit of $ ~~530~~ **653**. ~~6~~ **9** million. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of and seek regulatory approvals for our product candidates in our initial and potential additional indications as well as for other product candidates. We anticipate that our expenses will increase substantially if and as we: • continue to develop and conduct clinical trials, including in expanded geographies such as Europe, for our product candidates; • initiate and continue research and development, including preclinical, clinical and discovery efforts for any future product candidates; • seek to identify additional product candidates; • seek regulatory approvals for our product candidates that may successfully complete clinical development; • add operational, financial and management information systems and personnel, including personnel to support our product candidate development and help us comply with our obligations as a public company; • hire and retain additional personnel, such as clinical, quality control, scientific, commercial and administrative personnel; • maintain, expand and protect our intellectual property portfolio; • establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval; • add equipment and physical infrastructure to support our research and development; and • acquire or in- license other product candidates and technologies. Our expenses could increase beyond our expectations if we are required by the U. S. Food and Drug Administration, or the FDA, or other regulatory authorities to perform clinical trials in addition to those that we currently expect, or if there are any delays in establishing appropriate manufacturing arrangements for or in completing our clinical trials or the development of any of our product candidates. Risks Related to Future Financial Condition We will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts. Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the preclinical and clinical development of our current and future programs. If we are able to gain marketing approval for our product candidates, we will require significant additional amounts of cash in order to launch and commercialize such product candidates to the extent that such launch and commercialization are not the responsibility of a future collaborator that we may contract with in the future. In addition, other unanticipated costs may arise in the course of our development efforts. Because the design and outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of any product candidates we develop. Our future capital requirements depend on many factors, including: • the scope, progress, results and costs of researching and developing our current product candidates and other product candidates we may develop and pursue, including drug product manufacturing; • the timing and uncertainty of, and the costs involved in, obtaining marketing approvals for our current product candidates, and other product candidates we may develop and pursue; • the number of future product candidates that we may pursue and their development requirements; • the number of jurisdictions in which we plan to seek regulatory approvals; • if approved, the costs of commercialization activities for our product candidates for any approved indications, or any other product candidate that receives regulatory approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities; • subject to receipt of regulatory approval, revenue, if any, received from commercial sales of our product candidates for any approved indications or any other product candidates; • the extent to which we in- license or acquire rights to other products, product candidates or technologies; •

our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure; • the costs of preparing, filing and prosecuting patent applications and maintaining and protecting our intellectual property rights, including enforcing and defending intellectual property related claims; and • the ongoing costs of operating as a public company. We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. Any of our current or future license agreements may also be terminated if we are unable to meet the payment or other obligations under the agreements. **We** ~~Based on our current operating plan, we~~ believe that our **current** cash ~~,~~ **and** cash equivalents ~~and marketable securities as of December 31~~ , **which includes proceeds from our January** ~~2022~~ **2024** ~~may not~~ **public offering and at- the- market offerings, will** be sufficient to fund **our** ~~operations~~ - **operating expenditures** ~~for at least the next twelve months from the date of issuance of our consolidated financial statements which raises substantial doubt about the our ability to continue as a going concern,~~ and ~~we will need~~ **capital expenditure requirements necessary** to ~~obtain additional funding~~ **advance our research efforts and clinical trials into 2026** . Our estimate 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 sooner than planned ~~. In the event that we are unable to obtain sufficient additional funding, there can be no assurance that we will be able to continue as a going concern, and we will be forced to delay, reduce or discontinue our product candidate programs. If potential investors decline to participate in any future financings or potential collaborators decline to do business with us, our ability to increase our cash position may be limited. Furthermore, the price per share of our common stock could be materially adversely affected and our stockholders could lose part or all of their investment~~ . Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates. We expect our expenses to increase in connection with our planned operations. Unless and until we can generate a substantial amount of revenue from our product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings, collaborations, licensing arrangements or other sources, or any combination of the foregoing. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, our existing stockholders' ownership interests may be diluted, and the terms of these securities could include liquidation or other preferences and anti- dilution protections that could adversely affect the rights of our stockholders. In addition, debt financing, if available, may result in fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. 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 additional funds through collaborations or marketing, distribution, licensing and royalty arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, 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. We are a clinical- stage biopharmaceutical company with a very limited operating history and no products approved for commercial sale, which may make it difficult to evaluate our current business and predict our future success and viability. We are a clinical- stage biopharmaceutical company, focused on translating genetic insights into the development of therapies for CNS disorders characterized by neuronal imbalance. We commenced operations in 2016, have no products approved for commercial sale and have not generated any revenue from product sales. Our operations have been focused on developing and conducting preclinical and clinical studies of our product candidates. To date, we have not initiated or completed a pivotal clinical trial, obtained marketing approval for any product candidates, manufactured a commercial scale product or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Our limited operating history as a company makes any assessment of our future success and viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early- stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer. Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We have no products approved for commercial sale. To obtain revenues from the sales of our product candidates that are significant or large enough to achieve profitability, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing, and marketing our product candidates. Our ability to generate revenue and achieve profitability depends on many factors, including: • initiating and successfully completing research and preclinical and clinical development of our product candidates; • obtaining regulatory approvals ~~and marketing authorizations~~ for product candidates for which we successfully complete clinical development and clinical trials, if any; • developing a sustainable and scalable manufacturing process for our product candidates, as well as establishing and maintaining commercially viable supply relationships with third parties that can provide adequate products and services to support clinical activities and commercial demand of our product candidates; • identifying, assessing, acquiring and / or developing new product candidates; • negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; • launching and successfully commercializing product candidates for which we obtain regulatory ~~and marketing~~ approval, if any, either by collaborating with a partner or, if launched independently, by establishing a sales, marketing and distribution infrastructure; • obtaining and maintaining an adequate price for our product candidates in the countries where our products are commercialized, if any; • obtaining adequate reimbursement for our product candidates from payors; • obtaining market acceptance of our product candidates as viable treatment options; • addressing any competing technological and market developments; • receiving milestone and other payments under any future collaboration arrangements; • maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know- how; and • attracting, hiring and retaining qualified personnel. Because of the numerous risks and uncertainties associated with drug development, we are unable to predict the timing or amount of our expenses, or when we will be able to generate any meaningful revenue or achieve or maintain profitability, if ever. In addition, our expenses could increase beyond our current expectations if we are required by the FDA or foreign regulatory agencies to perform studies in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical trials or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with launching and commercializing any approved product candidate and ongoing compliance efforts. We may expend our limited resources on programs that do not yield a successful product candidate or fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Due to the significant resources required for the development of our programs and product candidates, we must focus our programs and product candidates on specific diseases and disease pathways and decide which product candidates to pursue and advance and the amount of resources to allocate to each. We are currently evaluating (i) ulixacaltamide for the treatment of essential tremor, or ET, ~~and Parkinson' s disease,~~ (ii) PRAX- ~~562~~ **628** for the treatment of **focal epilepsy** ~~SCN2A development and epileptic encephalopathy~~ , ~~or SCN2A- DEE, and SCN8A development and epileptic encephalopathy, or SCN8A- DEE;~~ (iii) PRAX- ~~222~~ **562** for the treatment of **SCN2A development and epileptic encephalopathy, or** SCN2A- DEE **, and SCN8A development and epileptic encephalopathy, or SCN8A- DEE** ; and (iv) ~~PRAX~~ **elsunersen for the treatment of SCN2A** - **DEE** ~~628 for the treatment of focal epilepsy~~ . Our drug development strategy is to clinically test and seek regulatory approval for our product candidates in indications in which we believe we will be able to efficiently generate proof- of- concept data. If any of our product candidates is approved, we then intend to expand to clinical testing and potentially seek regulatory approvals in other neurological disease indications based on genetic and mechanistic overlap with the primary indication. However, even if our product candidates are able to gain regulatory approval in one indication, there is no guarantee that we will be able to gain regulatory approval in another indication or expand to other indications. In addition, we may focus resources on pursuing indications outside of neurology based on the same strategic approach (e. g., human genetics, mechanistic rationale, the availability of translational tools, clinical development path, commercial opportunity) we utilize in determining on which of our discovery programs to focus. Our decisions concerning the allocation of research, development, collaboration, management and financial resources toward particular product candidates or therapeutic areas may not lead to the development of any viable commercial product and may divert resources away from better opportunities ~~. For example, in June 2022, we announced that we are undergoing a strategic realignment to focus resources on our ulixacaltamide, PRAX- 562, PRAX- 222 and PRAX- 628 programs, as well as our preclinical programs across our Cerebrum ™ and Solidus ™ platforms~~ . Additionally, we may reprioritize product candidate development plans and activities at any time and delay or terminate development of any product candidates we identify. Similarly, our potential decisions to delay, terminate or collaborate with third parties in respect of certain programs may subsequently also prove to be suboptimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the viability or market potential of any of our programs or product candidates or misread trends in the biopharmaceutical industry, in particular for neurological diseases, our business, financial condition, and results of operations could be materially adversely affected. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights. Risks Related to Research and Development and the Biopharmaceutical Industry Risks Related to Preclinical and Clinical Development The development and commercialization of drug products is subject to extensive regulation, and the regulatory approval processes of the FDA and comparable foreign **regulatory** authorities are lengthy, time- consuming, and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates on a timely basis if at all, our business will be substantially harmed. The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, import, marketing, distribution, adverse event reporting, including the submission of safety and other post- marketing information and reports, and other possible activities relating to our product candidates are subject to extensive regulation. In the United States, obtaining marketing approval for a new drug requires the submission of a New Drug Application, or NDA, to the FDA, and we are not permitted to market any product candidate in the United States until we obtain approval from the FDA of the NDA for that product candidate. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing, and controls. Outside the United States, many comparable foreign regulatory authorities employ similar approval processes. We have not previously submitted an NDA to the FDA or similar marketing authorization application to comparable foreign authorities, for any product candidate, and we cannot be certain that any of our product candidates will receive regulatory approval. Obtaining approval of an NDA can be a lengthy, expensive, and uncertain process, and as a company we have no experience with the preparation of an NDA submission or any other marketing authorization application. Our product candidates could fail to receive regulatory approval for many reasons, including the following: • the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials; • we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication; • the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval; • we may be unable to demonstrate that a product candidate' s clinical and other benefits outweigh its safety risks; • the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials; • the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere, or regulatory authorities may not accept a submission due to, among other reasons, the content or formatting of the submission; • the FDA or comparable foreign regulatory authorities may fail to approve our manufacturing processes or facilities or those of third- party manufacturers with which we contract for clinical and commercial supplies; and • the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval. This lengthy approval process, as well as the unpredictability of future clinical trial results, may result in our failing to obtain regulatory approval to market any of our product candidates, which would significantly harm our business, results of operations, and prospects. The FDA and comparable foreign regulatory authorities have substantial discretion in the approval process, and determining when or whether regulatory approval will be obtained for any of our product candidates. For example, regulatory authorities in various jurisdictions have in the past had, and may in the future have, differing requirements for, interpretations of and opinions on our preclinical and clinical data. As a result, we may be required to conduct additional preclinical studies, alter our proposed clinical trial designs, or conduct additional clinical trials to satisfy the regulatory authorities in each of the jurisdictions in which we hope to conduct clinical trials and develop and market our products, if approved. Further, even if we believe the data collected from clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA or any comparable foreign regulatory authority. In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post- marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates. Preclinical and clinical drug development involves a lengthy, complex and expensive process, with an uncertain outcome. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and the results of our clinical trials may not satisfy the requirements of the FDA or comparable foreign regulatory authorities. To obtain the requisite regulatory approvals to commercialize any product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our product candidates are safe and effective in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. In particular, pivotal clinical trials typically involve hundreds of patients, have significant costs and take years to complete. A product candidate can fail at any stage of testing, even after observing promising signs of activity in earlier preclinical studies or clinical trials. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later- stage clinical trials. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. **Certain of our** ~~Product~~ **product** candidates **failed to meet the primary endpoint** in later ~~stages~~ - **stage** ~~of~~ clinical trials **and we** may **in the future have product candidates that** fail to show the desired safety and efficacy ~~profile~~ **results in later stage clinical trials** despite having progressed through preclinical studies and initial clinical trials. ~~For example, in June 2022, we announced that the Phase 2 / 3 Aria Study evaluating the efficacy and safety of PRAX- 114 for monotherapy treatment of major depressive disorder did not achieve statistical significance on the primary endpoint of change from baseline in the 17- item Hamilton Depression Rating Scale total score at Day 15, or on any secondary endpoints.~~ There can be no assurance that any of our future clinical trials will ultimately be successful or support further clinical development of our product candidates. The commencement and rate of completion of preclinical studies and clinical trials for a product candidate may be delayed by many factors, including, for example: • inability to generate sufficient preclinical or other in vivo or in vitro data to support the initiation of clinical studies; • timely completion of preclinical laboratory tests, animal studies and formulation studies in accordance with the Good Laboratory Practice requirements and other applicable regulations of the U. S. Food and Drug Administration, or the FDA **, and comparable foreign regulatory authorities** ; • **delays in obtaining** approval **from** ~~by an~~ independent Institutional Review ~~Board~~ **Boards** , or ~~IRB~~ **IRBs** , or ethics ~~committee~~ **committees** at ~~each~~ **the** clinical ~~site~~ **sites** ~~before each~~ **we intend to utilize in our clinical** ~~trial~~ **trials** ~~may be initiated~~ ; • delays in reaching a consensus with regulatory agencies on study design and obtaining regulatory authorization to commence clinical trials; delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites; • delays in identifying, recruiting and training suitable clinical investigators; • delays in recruiting suitable patients to participate in our clinical trials; • delays in manufacturing, testing, releasing, validating or importing / exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing; • insufficient or inadequate supply or quality of product candidates or other materials necessary for use in clinical trials, or delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for clinical trials; • imposition of a temporary or permanent clinical hold by regulatory authorities; • developments on trials conducted by competitors for related technology that raises FDA or foreign regulatory authority concerns about risk to patients of the technology broadly, or if the FDA or a foreign regulatory authority finds that the investigational protocol or plan is clearly deficient to meet its stated objectives; • delays in recruiting, screening and enrolling patients and delays caused by patients withdrawing from clinical trials or failing to return for post- treatment follow- up; • delays caused by operational issues at clinical sites **or the use of a decentralized clinical trial model** ; • difficulty collaborating with patient groups and investigators; • failure by our CROs, other third parties or us to adhere to clinical trial protocols; **•** failure to perform in accordance with the FDA' s or any other regulatory authority' s Good Clinical Practice **, or**

GCP, requirements, or applicable regulatory guidelines in other countries; • occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits, or occurrence of adverse events in trials of the same class of agents conducted by other companies; • changes to the clinical trial protocols; • clinical sites deviating from trial protocol or dropping out of a trial; • changes in regulatory requirements and guidance that require amending or submitting new clinical protocols; • changes in the standard of care on which a clinical development plan was based, which may require new or additional trials; • selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data; • the cost of clinical trials of our product candidates being greater than we anticipated; • clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates; • transfer of manufacturing processes to larger- scale facilities operated by a contract development and manufacturing organization, or CDMO, and delays or failure by our CDMOs or us to make any necessary changes to such manufacturing process; and • third parties being unwilling or unable to satisfy their contractual obligations to us. Clinical trials must be conducted in accordance with the FDA and other applicable regulatory authorities' legal requirements, regulations or guidelines, and are subject to oversight by these governmental agencies and ethics committees or IRBs at the medical institutions where the clinical trials are conducted. Before commencing a clinical trial, the FDA or comparable foreign regulatory authorities could raise questions about or concerns with our proposed clinical protocol. For example, the FDA has previously issued clinical holds on certain of our product candidates, and we could not commence the respective clinical trial until such questions or concerns were resolved. We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by a Data Safety Monitoring Board for such trial or by the FDA or comparable foreign regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, we may need to amend clinical trial protocols that could require us to resubmit our clinical trial protocols to IRBs or ethics committees for reexamination, which may impact the costs, timing or successful completion of a clinical trial. Some of our trials are, have been, and may in the future be open- label studies, where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open- label clinical trials test only the investigational product candidate and sometimes do so at different dose levels. Open- label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open- label clinical trials are aware when they are receiving treatment. In addition, open- label clinical trials may be subject to an " investigator bias " where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. Therefore, it is possible that positive results observed in open- label trials will not be replicated in later placebo- controlled trials. Additionally, the trial design differences and placebo effects that may be possible in clinical research for the indications we are studying may make it difficult to extrapolate the results of earlier clinical trials to later clinical trials or to interpret the clinical data in any of our trials. In addition, we plan to conduct clinical trials of certain of our product candidates, including ulixacaltamide, utilizing novel primary endpoints for which the FDA and other regulatory authorities may have limited experience in interpreting and reviewing. Although we **have sought** ~~plan to seek~~ consensus with FDA and other regulatory authorities in connection with the design and implementation of our clinical studies, utilizing novel trial endpoints may increase the risk that the FDA and other regulatory authorities will consider the results from such trials, even if successful, insufficient to establish the safety or efficacy of our product candidates, which could require us to conduct additional studies beyond those we currently contemplate for our product candidates. Further, conducting clinical trials in foreign countries, such as the European Union **, or EU** , for our product candidates presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries. Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time 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 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. Delays in the completion of any preclinical studies or clinical trials of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate product revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Any delays to our preclinical studies or clinical trials that occur as a result could shorten any period during which we may have the exclusive right to commercialize our product candidates and our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, the FDA' s and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. **For instance, the regulatory**

landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state in which the clinical trial takes place, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application for multi- center trials. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state' s decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. The CTR foresees a three- year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR. Compliance with the CTR requirements by us and our third- party service providers, such as CROs, may impact our developments plans. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted. Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following regulatory approval, if obtained. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. In addition, many compounds that have initially showed promise in clinical or earlier stage testing are later found to cause undesirable or unexpected side effects that prevented further development of the compound. Additionally, the composition of our product candidates or learnings in preclinical studies or clinical trials may result in contraindications for any product candidates for which we may obtain regulatory approval. If unacceptable side effects arise in the development of our product candidates, we, foreign regulatory authorities, or the FDA, the IRBs or DSMBs at the institutions in which our trials are conducted could suspend or terminate our preclinical studies or clinical trials or foreign regulatory authorities or the FDA could order us to cease preclinical studies or clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment- emergent side effects that are deemed to be drug- related could also affect patient recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. Undesirable side effects in one of our clinical trials for our product candidates in one indication could adversely affect enrollment in clinical trials, regulatory approval and commercialization of our product candidates in other indications. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition to side effects caused by our product candidates, the administration process or related procedures of our product candidates could cause adverse side effects, such as the intrathecal or intravitreal administration process or related procedures for antisense oligonucleotide drugs, or ASOs. If any such adverse events occur, our clinical trials could be suspended or terminated. Even if we can demonstrate that adverse events are not product- related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the clinical trial. Additionally, other ASOs in clinical development utilizing intrathecal delivery could also generate data that could adversely affect the clinical, regulatory or commercial perception of our product candidates. Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, 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. Clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar products) after such approval, a number of potentially significant negative consequences could result, including: • regulatory authorities may withdraw or limit their approval of such product candidates; • regulatory authorities may require the addition of labeling statements, such as a Boxed Warning or contraindications; • we may be required to change the way such product candidates are distributed or administered, or change the labeling of the product candidates; • the FDA may require a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools, and regulatory authorities in other jurisdictions may require comparable risk mitigation plans; • we may be subject to regulatory investigations and government enforcement actions; • the FDA or a comparable foreign regulatory authority may require us to conduct additional clinical trials or costly post- marketing testing and surveillance to monitor the safety and efficacy of the product; • we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and • our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates, if approved, and significantly impact our ability to successfully commercialize our product candidates and generate revenues. If we encounter difficulties enrolling patients in our future clinical trials, our clinical development activities could be delayed or otherwise adversely affected. We have, and may in the future, experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. Patient enrollment is affected by many factors, including: • the patient eligibility criteria defined in the protocol; • the size and nature of the patient population ~~required for analysis of the trial' s primary endpoints~~ ; • in the case clinical trials focused on rare disease, the small size of the patient population and the potential of a patient being undiagnosed or misdiagnosed; • the proximity of patients to trial sites; • the design of the trial; • our ability to recruit clinical trial investigators with the appropriate competencies and experience; • competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications that we are investigating; • our ability to obtain and maintain patient consents; and • the risk that patients enrolled in clinical trials will drop out of the trials before completion. In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site. Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Delays in patient enrollment may result in increased costs, affect the timing or outcome of the planned clinical trials, product candidate development and approval process and jeopardize our ability to seek and obtain the regulatory approval required to commence product sales and generate revenue, which could prevent completion of these trials, adversely affect our ability to advance the development of our product candidates, cause the value of our company to decline and limit our ability to obtain additional financing if needed. ~~We are also required to register certain clinical trials and post the results of completed clinical trials on a government- sponsored database, such as ClinicalTrials. gov in the United States, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.~~ Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become 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 publicly disclose preliminary or topline data from our clinical trials, which are based on a preliminary analysis of then- available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline or preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the topline or preliminary data we previously reported. As a result, topline and preliminary data should be viewed with caution until the final data are available. From time to time, we ~~may also~~ disclose interim data from our preclinical studies and clinical trials. Interim data from clinical trials that we ~~may~~ complete 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. Adverse changes between interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. Others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the interim, preliminary or topline data that we report differ from later, final or actual results, or if others, including the FDA and comparable foreign regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects. The markets for our product candidates may be smaller than we expect. Our estimates of the potential market opportunities in each of our platforms include several key assumptions based on our industry knowledge, industry publications and third- party research reports and other data sources and estimates. There can be no assurance that any of these assumptions are, or will remain, accurate. If the actual markets identified for our product candidates, or for any other product candidate we may develop in the future, is smaller than we expect, our revenues, if any, may be limited and it may be more difficult for us to achieve or maintain profitability. We may not be successful in our efforts to identify or discover additional product candidates in the future. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development or commercialization for a number of reasons, including: • our inability to design such product candidates with the pharmacological or pharmacokinetic properties that we desire; or • potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be medicines that will receive marketing approval and achieve market acceptance. Research programs to identify new product candidates require substantial technical, financial and human resources. If we are unable to identify suitable compounds for preclinical and clinical development, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price. We conduct clinical trials for our product candidates in the United States, Europe and other jurisdictions, and the FDA, the European Medicines Agency, or EMA, and applicable foreign regulatory authorities may not accept data from trials conducted outside those respective jurisdictions. The acceptance of study data from preclinical studies and clinical trials conducted outside the United States may be subject to certain conditions for acceptance. For example, in cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States **, regardless of whether the trials were subject to an IND** , the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U. S. population and U. S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and the trials were performed by clinical investigators of recognized competence; and the data are considered valid without the need for an on- site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on- site inspection or other appropriate means. For trials that are conducted only at sites outside of the United States and not subject to an IND, the FDA requires the clinical trial to have been conducted in accordance with GCP and the FDA must be able to validate the data from the clinical trial through an on- site inspection if it deems such inspection necessary. For such trials not subject to an IND, the FDA generally does not review the clinical protocols for the trials, and therefore there is an additional potential risk that the FDA could determine that the trial design or protocol for a non- United States clinical trial was inadequate, which could require us to conduct additional clinical trials. Many foreign regulatory bodies, such as the EMA, 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, EMA or any applicable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA, EMA or any applicable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction. We obtained orphan drug designation for PRAX- 562 and **elsunersen** ~~PRAX- 222~~ and may plan to seek orphan drug designation for additional product candidates, but we may be unable to obtain or maintain such a designation or the benefits associated with orphan drug status, including marketing exclusivity, which may cause our revenue, if any, to be reduced. In the United States, under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200, 000 in the United States, or a patient population greater than 200, 000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug. Orphan drug designation must be requested and granted by the FDA before a new NDA is submitted. After the FDA grants orphan drug designation, it will disclose publicly the generic identity of the drug and its potential orphan use. **In the EU, the European Commission grants orphan designation on the basis of the EMA' s Committee for** Orphan ~~drug~~ **Medicinal Products opinion. A medicinal product may be** ~~designation~~ **designated** ~~does~~ **as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life- threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10, 000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would** not ~~convey any advantage~~ **generate sufficient return** in ~~, or shorten~~ **the EU to justify investment; and (3)** ~~the~~ **there** ~~duration~~ **exists no satisfactory method** of **diagnosis** , **prevention or treatment, of such condition authorized** ~~the regulatory review and approval process. The FDA granted orphan drug designation to PRAX- 562~~ for **marketing in** the **EU** ~~treatment of SCN2A- DEE and SCN8A- DEE~~ , ~~respectively, and to PRAX- 222 for~~ **or if such a method exists, the product will be of significant benefit to** ~~the~~ **those affected by the condition** ~~treatment of SCN2A- DEE~~. In the United States, orphan designation entitles a party to financial incentives such as opportunities for grant funding toward clinical trial costs, tax advantages and user- fee waivers. In addition, if a product candidate that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same product for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. The applicable exclusivity period is ten years in ~~Europe~~ **the EU** , but such exclusivity period can be reduced to six years if **, at the end of the fifth year,** a product no longer meets the criteria for orphan designation or if the product is sufficiently profitable that market exclusivity is no longer justified. **The FDA granted orphan drug designation to PRAX- 562 for the treatment of SCN2A- DEE and SCN8A- DEE, respectively, and to elsunersen for the treatment of SCN2A- DEE. We also obtained orphan designation in the EU for PRAX- 562 for the treatment of SCN2A- DEE and SCN8A- DEE, and for elsunersen for the treatment of SCN2A- DEE. We may seek orphan drug designation for other current and future product candidates.** Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA or comparable foreign regulatory authority can subsequently approve the same drug for the same condition if such regulatory authority concludes that the later drug is clinically superior because it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or comparable foreign regulatory authority later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar disease or condition containing a different active ingredient. In addition, if a subsequent drug is approved for marketing for the same or a similar disease or condition as any of our product candidates that receive marketing approval, we may face increased competition and lose market share regardless of orphan drug exclusivity. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. We received rare pediatric disease designation for PRAX- 562 and **elsunersen** ~~PRAX- 222~~. However, a marketing application for these product candidates, if approved, may not meet the eligibility criteria for a rare pediatric disease priority review voucher. In 2012, U. S. Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a " rare pediatric disease " that meets certain criteria may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the United States within one year following the date of approval. We received rare pediatric disease designation for PRAX- 562 for the treatment of SCN2A- DEE and SCN8A- DEE, and for **elsunersen** ~~PRAX- 222~~ for the treatment of SCN2A- DEE. Designation of a drug product as a product for a rare pediatric disease does not guarantee that a NDA for such drug product will meet the eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Under the Federal Food, Drug, and Cosmetic Act, or FDCA, we will need to request a rare pediatric disease priority review voucher in our original NDA for our product candidates for which we have received rare pediatric disease designation. The FDA may determine that a NDA for any such product candidates, if approved, do not meet the eligibility criteria for a priority review voucher. The authority for the FDA to award rare pediatric disease priority review vouchers for drug products after September 30, 2024 is currently limited to product candidates that receive rare pediatric disease designation on or prior to September 30, 2024, and the FDA may only award rare pediatric disease priority review vouchers through September 30, 2026. However, it is possible the authority for the FDA to award rare pediatric disease priority review vouchers will be further extended by Congress **. We received PRIME designation by the EMA for elsunersen and we may seek PRIME or other designations, schemes or tools in the EU for one or more of our product candidates, which we may not receive. Such designations may not lead to a faster development or regulatory review or approval process and do not increase the likelihood that our product candidates will receive marketing authorization. The PRIority Medicines, or PRIME, scheme was launched by the EMA in 2016. In the EU, innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the Breakthrough Therapy designation in the United States. PRIME is a voluntary scheme aimed at enhancing the EMA' s support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. The benefits of a PRIME designation include the appointment of a rapporteur before submission of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process. In November 2023, elsunersen was granted PRIME designation by the EMA' s Committee for Medicinal Products for Human Use, or CHMP, for the treatment of SCN2A- DEE. Acknowledging that elsunersen targets an unmet medical need, the EMA offers enhanced support in the development of the medicinal product through enhanced interaction and early dialogue to optimize our development plans and speed up regulatory evaluation in the EU. The PRIME designation does not, however, guarantee that the regulatory review process in the EU will be shorter or less demanding. Neither does the PRIME designation guarantee that the European Commission will grant a marketing authorization for elsunersen** . Risks Related to Regulatory Approval Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions. Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants approval of a product candidate, comparable regulatory authorities in other jurisdictions, including Australia and Europe, must also approve the manufacturing, marketing and sale of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must also be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to governmental approval. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we or any partner we work with fail to comply with the regulatory requirements in international markets or fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed. Our product candidates may be regulated as controlled substances, the making, use, sale, importation, exportation, and distribution of which are subject to significant regulation by the U. S. Drug Enforcement Administration, or DEA, and other regulatory agencies. Our product candidates may be classified as controlled substances, which are subject to state, federal, and foreign laws and regulations regarding their manufacture, use, sale, importation, exportation, and distribution. Among other things, controlled substances are regulated under the federal Controlled Substances Act of 1970, and regulations of the DEA. The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. Prior to commercialization, centrally acting drugs, such as those we are developing, are generally subject to review and potential scheduling by the DEA. It is possible that our product candidates may be regulated by the DEA as controlled substances, which would subject such product candidates to additional restrictions regarding their manufacture, shipment, storage, sale and use, depending on the scheduling of the active ingredients, and may limit the commercial potential of any of our product candidates, if approved. Various states also independently regulate controlled substances. Though state controlled substances laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule drugs as well. While some states automatically schedule a drug when the DEA does so, in other states there must be rule making or a legislative action. State scheduling may delay commercial sale of any controlled substance drug product for which we obtain federal regulatory approval and adverse scheduling could impair the commercial attractiveness of such product. We or our collaborators must also obtain separate state registrations in order to be able to obtain, handle and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions from the states in addition to those from the DEA or otherwise arising under federal law. For any of our product candidates classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. There is a risk that DEA regulations may limit the supply of the compounds used in clinical trials for our product candidates, and, in the future, the ability to produce and distribute our products in the volume needed to meet commercial demand. Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, recordkeeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of product candidates including controlled substances. The DEA, and some states, conduct periodic inspections of registered establishments that handle controlled substances. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of their restrictive nature, these regulations could limit commercialization of any of our product candidates that are classified as controlled substances. We could be subject to product liability lawsuits based on the use of our product candidates in clinical testing or, if obtained, following our products' marketing approval and commercialization. Product liability lawsuits brought against us or any of our future collaborators could divert our resources and attention, require us to cease clinical testing, cause us to incur substantial liabilities or limit commercialization of our product candidates. We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of biopharmaceutical products. Currently, we have no products that have been approved for commercial sale; however, the use of our product candidates by us and any collaborators in clinical trials may expose us to liability claims. We will face an even greater risk if product candidates are approved by regulatory authorities and introduced commercially. Product liability claims may be brought against us or our partners if any product candidate we develop allegedly causes injury or is found to be otherwise unsuitable for human use during product testing, manufacturing, marketing or sale. Any such product liability claim may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. Such claims could be made by participants enrolled in our clinical trials, patients, health care providers, biopharmaceutical companies, our collaborators or others using, administering or selling any of our future approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, product liability claims may result in: • decreased demand for any of our future approved products; • injury to our reputation; • withdrawal of clinical trial participants; • termination of clinical trial sites or entire trial programs; • significant litigation costs; • substantial monetary awards to, or costly settlements with, patients or other claimants; • product recalls or a change in the indications for which any approved drug products may be used; • loss of revenue; • diversion of management and scientific resources from our business operations; and • the inability to commercialize our product candidates. Although the clinical trial process is designed to identify and assess potential side effects, clinical development does not always fully characterize the safety and efficacy profile of a new medicine, and it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If our product candidates were to cause adverse side effects during clinical trials or after approval, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates. If any of our product candidates are approved for commercial sale, we will be highly dependent upon consumer perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity associated with illness or other adverse effects resulting from physicians' or patients' use or misuse of our products or any similar products distributed by other companies. Although we maintain product liability insurance coverage including clinical trial liability, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if we commercialize any product that receives regulatory approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects. We face significant competition in an environment of rapid technological and scientific change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer, more advanced or more effective than ours, which may negatively impact our ability to successfully market or commercialize any product candidates we may develop and ultimately harm our financial condition. The development and commercialization of new drug products is highly competitive. We may face competition with respect to any product candidates that we seek to develop or commercialize in the future from biopharmaceutical companies worldwide. Potential competitors also include 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. Specifically, we face competition with T- type calcium channel inhibitor programs in development targeting ET, including that of Jazz Pharmaceuticals, as well as other programs in clinical development targeting other mechanisms of action, **such as GABA by Sage Therapeutics,** and approved therapies, such as propranolol, and off- label therapies, such as primidone; and sodium channel blocker or similar programs in development for **focal epilepsy and** DEEs, including those of SK- Pharma, Xenon Pharmaceuticals, ~~Neurocrine Biosciences~~ and ~~Stoke Therapeutics~~ **Biohaven Pharmaceuticals** , as well as other programs in clinical development targeting other mechanisms of action **including those from Longboard Pharmaceuticals, Marinus Pharmaceuticals and Stoke Therapeutics** , and approved therapies including other existing ion channel blockers. If any of these competitors or competitors for our other product candidates receive FDA approval before we do, our product candidates would not be the first treatment on the market, and our market share may be limited. In addition to competition from other companies targeting our target indications, any products we may develop may also face competition from other types of therapies. Many of our current or potential competitors, either alone or with their strategic partners, have: • greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products; • more extensive experience in preclinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling drug products; • products that have been approved or are in late stages of development; and • collaborative arrangements in our target markets with leading companies and research institutions. Mergers and acquisitions in the biopharmaceutical industry may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Furthermore, currently approved products could be discovered to have application for treatment of our targeted disease indications or similar indications, which could give such products significant regulatory and market timing advantages over our product candidates. Our competitors also may obtain FDA or other comparable foreign regulatory approval for their products more rapidly than we may obtain approval for ours and may obtain orphan product exclusivity from the FDA for indications that we are targeting, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, products or technologies developed by our competitors may render our potential product candidates uneconomical or obsolete and we may not be successful in marketing any product candidates we may develop against competitors. In addition, we could face litigation or other proceedings with respect to the scope, ownership, validity and / or enforceability of our patents relating to our competitors' products and our competitors may allege that our products infringe, misappropriate or otherwise violate their intellectual property. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. Risks Related to the Commercialization of our Product Candidates Risks Related to Post- Marketing Regulatory Requirements Any product candidate for which we obtain marketing approval will be subject to extensive post- marketing regulatory requirements and could be subject to post- marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved. Even if the FDA or a comparable foreign regulatory authority approves any of our product candidates, we will be subject to ongoing regulatory requirements in the applicable jurisdictions for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record- keeping, conduct of post- marketing studies and submission of safety, efficacy and other post- market information. In addition, we will be subject to continued compliance with cGMP or similar regulatory requirements outside the United States and GCP requirements for any clinical trials that we conduct post- approval. Manufacturers and their facilities are required to comply with extensive regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to cGMP or other similar regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP or similar regulatory requirements and adherence to commitments made in any marketing application, and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control. Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post- marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the product candidate. In the United States, the FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long- term patient follow- up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Similar requirements may apply in foreign jurisdictions. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with requirements including submissions of safety and other post- marketing information and reports and registration. In the United States and elsewhere, the FDA and foreign regulatory authorities may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, or with our third- party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information or other restrictions; imposition of post- market studies or clinical trials to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS or similar program. Other potential consequences include, among other things: • restrictions on the manufacturing of our products, the approved manufacturers or the manufacturing process; • withdrawal of the product from the market or voluntary product recalls; • requirements to conduct post- marketing studies or clinical trials; • fines, restitution or disgorgement of profits or revenues; • warning or untitled letters from the FDA or comparable notice of violations from foreign regulatory authorities; • suspensions of any of our ongoing clinical trials; • refusal by the FDA or foreign regulatory authorities to approve pending applications or supplements to approved applications filed by us or suspension or withdrawal of marketing approvals; • product seizure or detention or refusal to permit the import or export of products; and • consent decrees, injunctions or the imposition of civil or criminal penalties. Violations of the FDCA relating to the promotion of prescription drugs may also lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws. Accordingly, to the extent we receive marketing approval for one or more of our product candidates, we and our third- party partners will continue to expend time, money and effort in all areas of regulatory compliance, including promotional and labeling compliance, manufacturing, production, product surveillance and quality control. Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products, if approved. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected. The policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow to, or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability. The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses. If we are found or alleged to have improperly promoted off- label uses, we may become subject to significant liability. The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about drug products. These regulations include standards and restrictions for direct- to- consumer advertising, industry- sponsored scientific and educational activities, promotional activities involving the internet and off- label promotion. For example, any regulatory approval that the FDA grants is limited to those indications and patient populations for which a drug is deemed to be safe and effective by the FDA. While physicians in the United States may choose, and are generally permitted, to prescribe products for uses that are not described in the product' s labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, our ability to promote any of our products candidates, if approved, will be narrowly limited to those indications and populations that are specifically approved by the FDA or such other regulatory agencies, and if we are found to have promoted such off- label uses, we may become subject to significant liability. For example, the federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off- label promotion. The government has also required companies to enter into consent decrees or imposed permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition. Risks Related to Sales, Marketing and Competition Our commercial success depends upon attaining significant market acceptance of our drug product candidates, if approved, among physicians, patients, third- party payors and other members of the medical community. Even if any of the product candidates we develop receives marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, third- party payors, such as Medicare and Medicaid programs and managed care organizations in the United States, and others in the medical community. In addition, the availability of coverage by third- party payors may be affected by existing and future health care reform measures designed to reduce the cost of health care. If the product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of any product candidate, if approved for commercial sale, will depend on a number of factors, including: • efficacy and potential advantages compared to alternative treatments; • the ability to offer our products, if approved, for sale at competitive prices; • relative convenience and ease of administration compared to alternative treatments; • perceptions by the medical community, physicians, and patients, regarding the safety and effectiveness of our products and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; • the size of the market for such product candidate, based on the size of the patient subsets that we are targeting, in the territories for which we gain regulatory approval; • the recommendations with respect to our product candidates in guidelines published by various scientific organizations applicable to us and our product candidates; • the strength of sales, marketing and distribution support; • the timing of any such marketing approval in relation to other product approvals; • any restrictions on concomitant use of other medications; • support from patient advocacy groups; • the ability to obtain sufficient third- party coverage and adequate reimbursement; and • the prevalence and severity of any side effects. If government and other third- party payors do not provide coverage and adequate reimbursement levels for any products we commercialize, market acceptance and commercial success would be reduced. The successful commercialization of our product candidates in the United States will depend in part on the extent to which third- party payors, including governmental authorities and private health insurers, provide coverage and adequate reimbursement levels, as well as implement pricing policies favorable for our product candidates. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue. Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. In the United States and in other countries, 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. The availability of coverage and adequacy of reimbursement for our products by third- party payors, including government health care programs (e. g., Medicare, Medicaid, TRICARE), managed care providers, private health insurers, health maintenance organizations and other organizations is essential for most patients to be able to afford medical services and biopharmaceutical products such as our product candidates. Third- party payors decide which medications they will pay for and establish reimbursement levels. In the United States, the Centers for Medicare & Medicaid Services, or CMS, an agency within the U. S. Department of Health and Human Services, or HHS, determines whether and to what extent new products will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree. Factors payors consider in determining reimbursement are based on whether the product is: • a covered benefit under its health plan; • safe, effective and medically necessary; • appropriate for the specific patient; • cost- effective; and • neither experimental nor investigational. Our ability to successfully commercialize our product candidates will depend in part on the extent to which coverage and adequate reimbursement for our products and related treatments will be available from third- party payors. Moreover, a payor' s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. If coverage and adequate reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment. In the United States, no uniform policy for coverage and reimbursement for products exists among third- party payors. Therefore, coverage and reimbursement for our products can differ significantly from payor to payor. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. One payor' s determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product. Third- party payors may also limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA- approved products for a particular indication. We cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates. A decision by a third- party payor not to cover or not to separately reimburse for our medical products or therapies using our products could reduce physician utilization of our products once approved. Assuming there is coverage for our product candidates, or therapies using our product candidates by a third- party payor, the resulting reimbursement payment rates may not be adequate or may require co- payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States will be available for our current or future product candidates, or for any procedures using such product candidates, and any reimbursement that may become available may not be adequate or may be decreased or eliminated in the future. Further, increasing efforts by third- party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost- effectiveness of our products, in addition to the costs required to obtain FDA or comparable regulatory approvals. Additionally, we may also need to provide discounts to purchasers, private health plans or government healthcare programs. Our product candidates may nonetheless not be considered medically necessary or cost- effective. If third- party payors do not consider a product to be cost- effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. We expect to experience pricing pressures from third- party payors in connection with the potential sale of any of our product candidates. Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any. In some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, in the **EU** ~~European Union~~, member states can restrict the range of medicinal products for which their national health insurance systems provide reimbursement and they can control the prices of medicinal products for human use. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Approaches between member states are diverging. For example, in France, effective market access will be supported by agreements with hospitals and products may be reimbursed by the Social Security Fund. The price of reimbursed medicines is negotiated with the Economic Committee for Health Products, or CEPS. There can be no assurance that any country that has price controls or reimbursement limitations for biopharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates. Historically, products launched in the **EU** ~~European Union~~ do not follow price structures of the United States and generally prices tend to be significantly lower. Even if we obtain approval of any of our product candidates in the United States or Europe, we may never obtain approval or commercialize such products in other countries, which would limit our ability to realize their full market potential. In order to market any products in the United States or Europe, we must establish and comply with numerous and varying regulatory requirements regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approvals outside of where our clinical trials currently have been conducted could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials which would be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. Satisfying these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. In addition, our failure to obtain regulatory approval in any country may delay or have negative effects on the process for regulatory approval in other countries. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, our ability to realize the full market potential of our products will be harmed. We currently have no marketing and sales organization and have no experience as a company in commercializing products, and we may have to invest significant resources to develop these capabilities. If we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if approved, we may not be able to generate product revenue. We have no internal sales, marketing or distribution capabilities, nor have we commercialized a product. If any of our product candidates ultimately receives regulatory approval, we expect to establish a marketing and sales organization with technical expertise and supporting distribution capabilities to commercialize each such product in major markets, which will be expensive and time consuming. We have no prior experience as a company in the marketing, sale and distribution of biopharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. We may also choose to collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. We may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. In addition, our product revenues and our profitability, if any, may be lower if we rely on third parties for these functions than if we were to market, sell and distribute any products that we develop ourselves. 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 products effectively. If we are not successful in commercializing our products, either on our own or through arrangements with one or more third parties, we may not be able to generate any future product revenue and we would incur significant additional losses. Risks Related to Ongoing Regulatory and Legal Compliance Risks Related to Healthcare and Related Laws Our relationships with healthcare providers and physicians and third- party payors will be subject to applicable anti- kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Although we do not currently have any products on the market, upon commercialization of our product candidates, if approved, we will be subject to additional healthcare statutory and regulatory requirements and oversight by federal and state governments in the United States as well as foreign governments in the jurisdictions in which we conduct our business. Healthcare providers, physicians and third- party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third- party payors, customers and others may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. In particular, the research of our product candidates, as well as the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self- dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission (s), certain customer incentive programs and other business or financial arrangements. The applicable federal, state and foreign healthcare laws and regulations laws that may affect our ability to operate include, but are not limited to: • the federal Anti- Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. The term remuneration has been interpreted broadly to include anything of value. Further, courts have found that if " one purpose " of remuneration is to induce referrals, the federal Anti- Kickback statute is violated. The Anti- Kickback Statute has been interpreted to apply to arrangements between biopharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution; • the federal civil and criminal false claims laws, including the FCA, and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false, fictitious or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs; knowingly making, using or causing to be made or used, a false record or statement material to a false, fictitious or fraudulent claim or an obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. In addition, a claim that includes items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim under the FCA. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to " cause " the submission of false or fraudulent claims.

The FCA also permits a private individual acting as a " whistleblower " to bring qui tam actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery or settlement; • ~~the federal Health Insurance Portability and Accountability Act of 1996, or~~ HIPAA, which created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third- party payors, or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e. g., public or private), and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false fictitious or fraudulent statement or entry in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti- Kickback Statute, a person or entity can be found guilty of violating HIPAA fraud provisions without actual knowledge of the statute or specific intent to violate it; • the federal Physician Payments Sunshine Act and its implementing regulations, which require manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program (with certain exceptions) to report annually to CMS information related to direct or indirect payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non- physician providers including physician providers including physician assistants and nurse practitioners, and teaching hospitals, as well as ownership and investment interests held by the physicians and their immediate family members; • federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and • analogous U. S. state, local and foreign laws and regulations, such as state anti- kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by any third- party payor, including private insurers, and may be broader in scope than their federal equivalents; state and foreign laws that require biopharmaceutical companies to comply with the biopharmaceutical industry' s voluntary compliance guidelines and other relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; and state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing; state and local laws that require the registration of biopharmaceutical sales representatives. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource- consuming and can divert a company' s attention from the business. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management' s attention from the operation of our business. The shifting compliance environment and the need to build and maintain robust and expandable systems to comply with multiple jurisdictions with different compliance or reporting requirements increases the possibility that a healthcare company may run afoul of one or more of the requirements. It is possible that governmental and enforcement authorities will conclude that our business practices, including our arrangements with physicians and other healthcare providers, some of whom may receive stock options as compensation for services provided, may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to significant sanctions, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, reputational harm, exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non- compliance with these laws. Further, 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 similar penalties. Any action for violation of these laws, even if successfully defended, could cause us to incur significant legal expenses and divert management' s attention from the operation of the business. In addition, the approval and commercialization of any product candidate we develop outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. All of these could harm our ability to operate our business and our financial results. We may be subject to, or may in the future become subject to, U. S. federal and state, and foreign laws and regulations imposing obligations on how we collect, use, disclose, store and process personal information. Our actual or perceived failure to comply with such obligations could result in liability or reputational harm and could harm our business. Ensuring compliance with such laws could also impair our efforts to maintain and expand our customer base, and thereby decrease our revenue. The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of personal information, such as information that we may collect in connection with clinical trials in the United States and abroad. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or ~~perception~~ **perceptions** of their requirements may have on our business. This evolution may create uncertainty in our business, affect our ability to operate in certain jurisdictions or to collect, store, transfer use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or ~~regulation~~ **regulations** , our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our operations, financial performance and business. In Europe, the ~~General Data Protection Regulation, or~~ GDPR ~~,~~ took effect in May 2018. The GDPR imposes stringent requirements on entities that process personal data of individuals in the European Economic Area, or EEA. These requirements include, for example, establishing a legal basis for processing, providing notice to data subjects about how personal data is collected and processed, developing procedures to vindicate expanded data subject rights, implementing appropriate technical and organizational measures to safeguard personal data, introducing the obligation to notify data protection regulators or supervisory authorities (and in certain cases, affected individuals) of significant data breaches, imposing limitations on retention of personal data, maintaining a record of data processing and complying with the principal of accountability and the obligation to demonstrate compliance through policies, procedures, training and audit. In addition, the GDPR establishes obligations for entities that process " special categories " of personal data, such as health data. Nearly all clinical trials involve the processing of these " special categories " of personal data, and processing of personal data collected during the course of clinical trials is therefore subject to heightened protections under the GDPR. Violations of the GDPR can lead to potential fines of up to € 20 million or 4 % of the annual global revenues of the noncompliant undertaking, whichever is greater. In addition to the foregoing, a breach of the GDPR could result in regulatory investigations, reputational damage, orders to cease / change our processing of our data, enforcement notices, and / or assessment notices (for a compulsory audit). We may also face civil claims including representative actions and other class action type litigation (where individuals have suffered harm), potentially amounting to significant compensation or damages liabilities, as well as associated costs, diversion of internal resources, and reputational harm. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States, and the efficacy and longevity of current transfer mechanisms between the **EEA** ~~European Union~~ and the United States remains uncertain. ~~For example, in 2016,~~ **Case law from the Court of Justice of** the European Union ~~and United States agreed to a transfer framework for data transferred from the European Union to the United States called the Privacy Shield, but in July 2020 the Court of Justice of the EU~~ , or the CJEU, ~~limited how organizations could lawfully transfer personal data from the EEA to the United States~~ **states that reliance** ~~by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions~~ on ~~use of~~ the standard contractual clauses, or SCCs **— a standard form** ~~. While the CJEU upheld the adequacy~~ of **contract approved by** ~~the SCCs, it made clear that reliance on them~~ - **the European Commission as an adequate personal data transfer mechanism —** alone may not necessarily be sufficient in all circumstances. Use of the SCCs must now be assessed on a case- by- case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals and additional measures and / or contractual provisions may need to be put in place, however, the nature of these additional measures is currently uncertain. The ~~CJEU went on to state that if a competent supervisory authority believes that the SCCs cannot be complied with in the destination country and the required level of protection cannot be secured by other means, such supervisory authority is under an obligation to suspend or prohibit that transfer. The~~ European Commission ~~issued revised SCCs~~ **adopted its Adequacy Decision in relation to the new EU- U. S. Data Privacy Framework, or DPF,** on ~~June 4~~ **July 10** , ~~2021~~ **2023 , rendering** ~~to account for~~ the **DPF effective as a GDPR** ~~decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers~~ - **transfer** ~~from September 27, 2021; existing~~ **mechanism to U. S. entities self- certified under the DPF. We currently rely on the EU** standard contractual clauses **and** ~~arrangements must be migrated to~~ the ~~revised~~ **UK Addendum to the EU standard contractual** clauses ~~by December 27, 2022. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers~~ to ~~non-EEA entities subject to the GDPR. The revised SCCs apply only to the~~ transfer ~~of~~ personal data outside ~~of~~ the EEA and ~~not~~ **the UK, including to** the United ~~Kingdom~~ **States** , ~~or the U~~ **with respect to both intragroup and third party transfers** . **The existing legal complexity and uncertainty regarding international personal** ~~K.; the U. K.' s Information Commissioner' s Office launched a public consultation on its draft revised~~ data transfers ~~mechanisms~~ **may continue, and** in ~~August 2021~~ **particular, the DPF Adequacy Decision could be challenged and international transfers to the United States and to other jurisdictions more generally could continue to be subject to enhanced scrutiny by regulators** . As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and / or start taking enforcement action, we could suffer additional costs, complaints and / or regulatory investigations or fines, and / or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. Further, since January 2021, we may also be subject to the **UK** ~~U. K.~~ GDPR, which, together with the UK Data Protection Act 2018, retains the GDPR in **UK** ~~U. K.~~ national law. The **UK** ~~U. K.~~ GDPR mirrors the fines under the GDPR, meaning the potential of parallel fines of up to the greater of £ 17. 5 million or 4 % of **a non- compliant undertaking' s** global ~~turnover~~ **annual revenue for the preceding financial year. On October 12, 2023, the UK Extension to the DPF came into effect (as approve by the UK government) as a data transfer mechanism from the UK to U. S. entities self- certified under the DPF** . The European Commission has adopted an adequacy decision in favor of the United Kingdom, enabling data transfers from EU member states to the United Kingdom without additional safeguards. However, the **UK** ~~U. K.~~ adequacy decision will automatically expire in June 2025 unless the European Commission re- assesses and renews / extends that decision and remains under review by the Commission during this period. In September 2021, the **UK** ~~U. K.~~ government launched a consultation on its proposals for wide- ranging reform of **UK** ~~U. K.~~ data protection laws following Brexit. There is a risk that any material changes which are made to the **UK** ~~U. K.~~ data protection regime could result in the European Commission reviewing the **UK** ~~U. K.~~ adequacy decision, and the **UK** ~~United Kingdom~~ losing its adequacy decision if the European Commission deems the **UK** ~~United Kingdom~~ to no longer provide adequate protection for personal data. The relationship between the **UK** ~~United Kingdom~~ and the **EU** ~~European Union~~ in relation to certain aspects of data protection law remains uncertain, and it is unclear how **UK** ~~U. K.~~ data protection laws and regulations will develop in the medium to longer term. In the United States, HIPAA establishes a set of national privacy and security standards for the protection of individually identifiable health information, including protected health information, or PHI, by health plans, certain health care clearinghouses and health care providers that submit certain covered transactions electronically, or covered entities, and their " business associates, " which are persons or entities that perform certain services for, or on behalf of, a covered entity that involve creating, receiving, maintaining or transmitting PHI, as well as their covered subcontractors. While we do not believe that we are currently acting as a covered entity or business associate under HIPAA, we may receive individually identifiable health information from these entities. Failure to receive this information properly could subject us to HIPAA' s criminal penalties. Further, any person may be prosecuted under HIPAA' s criminal provisions either directly or under aiding- and- abetting or conspiracy principles. Depending on the facts and circumstances, we could face substantial criminal penalties if we knowingly receive individually identifiable health information from a HIPAA- covered healthcare provider or research institution that has not satisfied HIPAA' s requirements for disclosure of individually identifiable health information. In addition, responding to government investigations regarding alleged violations of these and other laws and regulations, even if ultimately concluded with no findings of violations or no penalties imposed, can consume company resources and impact our business and, if public, harm our reputation. Various states, such as California and Massachusetts, have also implemented similar privacy laws and regulations, such as the California Confidentiality of Medical Information Act, or the CMIA, that impose restrictive requirements regulating the use and disclosure of health information and other personally identifiable information. In addition to imposing fines and penalties, some of these state laws afford private rights of action to individuals who believe their personal information has been misused. California' s patient privacy laws, for example, provide for significant penalties and permit injured parties to sue for damages. In addition to the CMIA, California also enacted the ~~California Consumer Privacy Act of 2018, or~~ CCPA, which went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability ~~, and many similar laws have been proposed at the federal level and in other states~~ . Further, the ~~California Privacy Rights Act, or~~ CPRA, which generally went into effect on January 1, 2023, significantly amends the CCPA and imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also ~~creates~~ **created** a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may be required. Similar laws have been passed in ~~Virginia, Colorado, Connecticut and Utah, and have been proposed in~~ other states **,** and **are continuing to be proposed** at the **state and** federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition. ~~Furthermore, the Federal Trade Commission, or the FTC, and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive. For example, according to the FTC, failing to take appropriate steps to keep consumers' personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5 (a) of the Federal Trade Commission Act. The FTC expects a company' s data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities.~~ The interplay of federal and state laws may be subject to varying interpretations by courts and government agencies, creating complex compliance issues for us and potentially exposing us to additional expense, adverse publicity and liability. Further, as regulatory focus on privacy issues continues to increase and laws and regulations concerning the protection of personal information expand and become more complex, these potential risks to our business could intensify. The legislative and regulatory landscape for privacy and data security continues to evolve, and there has been an increasing focus on privacy and data security issues which may affect our business. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, collaborators, or other third parties to comply with current and future laws and regulations could result in government enforcement actions (including the imposition of significant penalties), criminal and / or civil liability for us and our officers and directors, private litigation and / or adverse publicity that negatively affects our business. Ongoing healthcare legislative and regulatory reform measures may have a material adverse effect on our business and results of operations. In the United States and in some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative initiatives and regulatory changes regarding the healthcare system directed at broadening the availability of healthcare, improving the quality of healthcare, and containing or lowering the cost of healthcare. For example, in March 2010, the ACA was enacted, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacted the U. S. biopharmaceutical industry. The ACA, among other things, subjects biological products to potential competition by lower- cost biosimilars, expands the types of entities eligible for the 340B drug discount program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations; established annual fees and taxes on manufacturers of certain branded prescription drugs; and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50 % (increased to 70 % pursuant to the Bipartisan Budget Act of 2018, or BBA, effective as of January 2019) point- of- sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’ s outpatient drugs to be covered under Medicare Part D. Since its enactment, there have been numerous judicial, administrative, executive and legislative challenges to certain aspects of the ACA. On June 17, 2021 the U. S. Supreme Court dismissed the recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Thus, the ACA will remain in effect in its current form. ~~Further, prior to the U. S. Supreme Court ruling, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.~~ In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, on August 2, 2011, the Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through ~~2030~~ **2032** , with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Moreover, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which ~~eliminates~~ **eliminated** the statutory Medicaid drug rebate cap ~~, currently set at 100 % of a drug’ s AMP,~~ for single source and innovator multiple source drugs, beginning January 1, 2024 **. The rebate was previously capped at 100 % of a drug' s average manufacturer price** . Payment methodologies may also be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their products. Such scrutiny has resulted in several recent U. S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. By way of example, in August 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law. 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 Department of Health and Human Services **, or HHS,** to implement many of these provisions through guidance, as opposed to regulation, for the initial years. ~~For~~ **HHS has and will continue to issue and update guidance as these programs are implemented. These provisions started to take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs** that ~~and~~ **will be subject to price negotiations, although** ~~other~~ -- **the** ~~reasons, it~~ **Medicare drug price negotiation program** is currently **subject to legal challenges. In addition, in response to the Biden administration’ s October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the Center for Medicare and Medicaid Innovation which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is** unclear ~~how~~ **whether** the ~~IRA~~ **models** will be ~~effectuated, or~~ **utilized in any health reform measures in** the **future** ~~impact of the IRA on our business~~. At the state level in the United States, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biologic 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. Legally mandated price controls on payment amounts by third- party payors or other restrictions on coverage or access could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates that we successfully commercialize or put pressure on our product pricing. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States or in any other jurisdictions. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability. In the United States, inadequate funding for the FDA, the SEC, and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business. The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs and or modifications to approved drugs or to be reviewed and / or 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 FDA employees and stop critical activities. Separately, in response to the COVID- 19 pandemic, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points. Even though the FDA has since resumed standard inspection operations of domestic facilities ~~where feasible~~ , ~~the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID- 19 pandemic, and~~ any resurgence of the virus or emergence of new variants may lead to ~~further~~ inspectional **or administrative** delays ~~. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID- 19 pandemic~~ . If a prolonged government shutdown occurs, or if global health concerns ~~continue to~~ hinder or prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Risks Related to International Regulations EU drug marketing and reimbursement regulations may materially affect our ability to market and receive coverage for our products in the European member states. We ultimately intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of drugs is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third- party payors for our product candidates and may be affected by existing and future health care reform measures. Much like the federal Anti- Kickback Statute prohibition in the United States, 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** ~~European Union~~ . The provision of benefits or advantages to physicians is governed by the national laws of EU member states, and in respect of the United Kingdom (which is longer a member of the **EU** ~~European Union~~), the U. K. Bribery Act of 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 must often be subject to a prior notification and / or 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. In addition, the requirements governing drug pricing and reimbursement vary widely from country to country. For example, the **EU** ~~European Union~~ provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Reference pricing used by various EU member states and parallel distribution, or arbitrage between low- priced and high- priced member states, can further reduce prices. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. In some countries, we may be required to conduct a clinical study or other studies that compare the cost- effectiveness of any of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. There can be no assurance that any country that has price controls or reimbursement limitations for biopharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the **EU** ~~European Union~~ do not follow price structures of the United States and generally prices tend to be significantly lower. Publication of discounts by third- party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales and the potential profitability of any of our product candidates in those countries would be negatively affected. In the EU, similar developments may affect our ability to profitably commercialize our product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever- increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post- approval activities and affect our ability to commercialize our product candidates, if approved. In markets outside of the United States and EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In December 2021, Regulation No 2021 / 2282 on Health Technology Assessment, or HTA, amending Directive 2011 / 24 / EU, was adopted. ~~This~~ **While the** ~~regulation~~ **Regulation** ~~which~~ entered into force in January 2022 ~~and~~ **, it** will ~~become applicable~~ **only begin to apply** from January 12, 2025 onwards, **with preparatory and implementation- related steps to take place in the interim. Once applicable, it will have a phased implementation depending on the concerned products. The Regulation** intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and ~~providing~~ **provide** the basis for cooperation at ~~the~~ EU level for joint clinical assessments in these areas. **It** ~~The regulation foresees a three-year transitional period and~~ will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the ~~most~~ **highest** potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non- clinical (e. g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. Legal, political and economic uncertainty surrounding the exit of the United Kingdom from the European Union may be a source of instability in international markets, create significant currency fluctuations, adversely affect our operations in the United Kingdom and pose additional risks to our business, revenue, financial condition and results of operations. **Following** ~~In 2016, the United Kingdom held a referendum in which a majority of the eligible members of the electorate voted to leave the European Union, commonly referred to as~~ Brexit ~~. Pursuant to Article 50 of the Treaty on EU~~ , ~~the United Kingdom ceased being an~~ **and** ~~EU member state on January 31, 2020. On December 30, 2020, the United Kingdom and European Union signed the Trade and Cooperation Agreement, or TCA, which includes an agreement on free trade between the two parties and has been provisionally applicable~~ since January 1, 2021 ~~. Since January 1, 2021~~ , the United Kingdom **, or UK,** has operated under a separate regulatory regime to the **EU** ~~European Union~~ . EU laws regarding medicinal products only apply in respect of the **UK** ~~United Kingdom~~ to Northern Ireland (as set out in the Protocol on Ireland / Northern Ireland **, or the Protocol**) **. However, on February 27, 2023, the UK government and the European Commission reached a political agreement in the " Windsor Framework " to address discrepancies in the Protocol' s operation. This new framework fundamentally changes the existing system under the Protocol, including with respect to the regulation of medicinal products in the UK. In particular, the MHRA will be responsible for approving all medicinal products destined for the UK market (i. e., Great Britain and Northern Ireland), and the EMA will no longer have any role in approving medicinal products destined for Northern Ireland. A single UK-wide MA will be granted by the MHRA for all medicinal products to be sold in the UK, enabling products to be sold in a single pack and under a single authorization throughout the UK. The Windsor Framework was approved by the EU-UK Joint Committee on March 24, 2023, and the UK government and the EU will enact legislative measures to bring it into law. On June 9, 2023, the MHRA announced that the medicines aspects of the Windsor Framework will apply from January 1, 2025** . The EU laws that have been transposed into **UK** ~~U. K.~~ law through secondary legislation remain applicable as " retained EU law ~~.~~ **;** " ~~However~~ **however** , ~~under the Retained~~ EU ~~Law (Revocation and Reform) Bill 2022, which is currently before the U. K. parliament, any retained EU law~~ **laws that have taken effect since Brexit do** not **apply** ~~expressly preserved and " assimilated " into domestic law or extended by ministerial regulations (to no later than 23 June 2026) will automatically expire and be revoked by December 31, 2023. In addition, new EU legislation will not be applicable~~ in Great Britain **(England, Scotland and Wales)** . ~~The~~ **A Trade and Cooperation Agreement, or** TCA **, was agreed to between the UK and EU to facilitate continuing free trade between the parties, and** includes specific provisions concerning medicinal products, which include the mutual recognition of Good Manufacturing Practice, or GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued (such mutual recognition can be rejected by either party in certain circumstances), but does not foresee wholesale mutual recognition of U. K. and EU pharmaceutical regulations. Therefore, there remains political and economic uncertainty regarding to what extent the regulation of medicinal products will differ between the **UK** ~~United Kingdom~~ and the EU in the future. The **UK** ~~U. K.~~ government has passed **the** ~~a new~~ Medicines and Medical Devices Act 2021, which ~~introduces~~ **introduced** delegated powers in favor of the Secretary of State or an ' appropriate authority' to amend or supplement existing regulations in the area of medicines and medical devices. This allows new rules to be introduced in the future by way of secondary legislation, which aims to allow flexibility in addressing regulatory gaps. There is a possibility that over time, national laws will be amended and that consequently the regulatory framework in Great Britain will diverge from that of the EU. Any divergences will increase the cost and complexity of running our business, including with respect to the conduct of clinical trials. Since a significant proportion of the regulatory framework in the **UK** ~~United Kingdom~~ applicable to our business and our drug candidates is derived from EU directives and regulations, Brexit could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our drug candidates in the **UK** ~~United Kingdom~~ or the **EU** ~~European Union~~ . Great Britain ~~(England, Scotland and Wales)~~ is no longer covered by the **EU** ~~European Union~~ ' s procedures for the grant of marketing authorizations (Northern Ireland is **currently** covered by the centralized authorization procedure and can be covered under the decentralized or mutual recognition procedures). A separate marketing authorization will be required to market medicinal products in Great Britain. As of January 1, 2021, the Medicines and Healthcare Products regulatory Agency, or MHRA, is the **UK** ~~United Kingdom~~ ' s standalone medicines and medical devices regulator. It is currently unclear whether the MHRA is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, could prevent us and our collaborators or delay us and our collaborators from commercializing our drug candidates in the **UK** ~~United Kingdom~~ and / or the EEA and restrict our ability to generate revenue and achieve and sustain profitability. The uncertainty concerning the **UK** ~~United Kingdom~~ ' s legal, political and economic relationship with the **EU** ~~European Union~~ after Brexit may be a source of instability in the international markets, create significant currency fluctuations and / or otherwise adversely affect trading agreements or similar cross- border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise) beyond the date of Brexit. These developments, or the perception that any of them could occur, may have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U. K. financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Such a withdrawal from the **EU** ~~European Union~~ is unprecedented, and it is unclear how the **UK** ~~United Kingdom~~ ' s access to the European single market for goods, capital, services and labor within the **EU** ~~European Union~~, or single market, and the wider commercial, legal and regulatory environment, will impact our current and future operations (including business activities conducted by third parties and contract manufacturers on our behalf) and clinical activities in the **UK** ~~United Kingdom~~. Additional laws and regulations governing international operations could negatively impact or restrict our operations. For our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The U. S. Foreign Corrupt Practices Act, or the FCPA, prohibits any U. S. individual or business entity from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the biopharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals and healthcare providers in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Recently the SEC and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents or contractors, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non- U. S. nationals, of information products classified for national security purposes, as well as certain products, technology and technical data relating to those products. If we continue and expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers or our employees, the closing down of our facilities, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our products, if approved, in one or more countries and could materially damage our reputation, our brand, our international expansion efforts, our ability to attract and retain employees and our business, prospects, operating results and financial condition. The SEC also may suspend or bar issuers from trading securities on U. S. exchanges for violations of the FCPA' s accounting provisions. 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 harm 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. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our 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 for failure to comply with such laws and regulations. We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Environmental laws and regulations may impair our research, development or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions. Risks Related to Our Intellectual Property Risks Related to Licensed Intellectual Property Our success depends in part on our ability to protect our intellectual property. It is difficult and costly to protect our proprietary rights and technology, and we may not be able to ensure their protection. Our business depends in large part on obtaining and maintaining patent, trademark and trade secret protection of our proprietary technologies and our product candidates, their respective components, synthetic intermediates, formulations, combination therapies and methods used to manufacture them and methods of treatment, as well as successfully defending these patents against third- party challenges. Our ability to stop unauthorized third parties from making, using, selling, offering to sell or importing our product candidates is dependent upon the extent to which we have rights under valid and enforceable patents that cover these activities and whether a court would issue an injunctive remedy. If we are unable to secure and maintain patent protection for any product or technology we develop, or if the scope of the patent protection secured is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to commercialize any product candidates we may develop may be adversely affected. The patenting process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications, or obtain, maintain and / or enforce patents or trademarks that may issue or be registered based on our applications, at a reasonable cost or in a timely manner. In addition, our pending and future patent applications may not result in issued patents that protect our technology or products, in whole or in part, or may not effectively prevent others from commercializing competitive technologies and products. Changes in either patent laws or interpretation of patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. Further, we may not pursue, obtain, or maintain patent protection in all relevant markets. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non- disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach these agreements and disclose such results before a patent application is filed, thereby jeopardizing our ability to obtain patent protection. Moreover, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from or license to third parties and are reliant on our licensors or licensees. The strength of patents in the biotechnology and biopharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in- license may fail to result in issued patents with claims that cover our product candidates or uses thereof in the United States or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our technology, including our product candidates, or prevent others from designing around our claims. If the breadth or strength of protection provided by the patent applications that we hold with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop new or improved products and threaten our ability to commercialize our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced. We cannot be certain that we were the first to file any patent application related to our technology, including our product candidates, and, if we were not, we may be precluded from obtaining patent protection for our technology, including our product candidates. We cannot be certain that we are the first to invent the inventions covered by pending patent applications and, if we are not, we may be subject to priority disputes. Furthermore, for United States applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third- party or instituted by the United States Patent and Trademark Office, or USPTO, to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. Similarly, for United States applications in which at least one claim is not entitled to a priority date before March 16, 2013, derivation proceedings can be instituted to determine whether the subject matter of a patent claim was derived from a prior inventor' s disclosure. We may be required to disclaim part or all of the term of certain patents or all of the term of certain patent applications. There may be prior art of which we are not aware that may affect the validity or enforceability of a patent or patent application claim. There also may be prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. No assurance can be given that if challenged, our patents would be declared by a court to be valid or enforceable or that even if found valid and enforceable, would adequately protect our product candidates, or would be found by a court to be infringed by a competitor' s technology or product. We may analyze patents or patent applications of our competitors that we believe are relevant to our activities, and consider that we are free to operate in relation to our product candidates, but our competitors may achieve issued claims, including in patents we consider to be unrelated, which block our efforts or may potentially result in our product candidates or our activities infringing such claims. The possibility exists that others will develop products which have the same effect as our products on an independent basis which do not infringe our patents or other intellectual property rights, or will design around the claims of patents that may issue that cover our products. Recent or future patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. Under the Leahy- Smith America Invents Act, or America Invents Act, enacted in 2013, the United States moved from a " first to invent " to a " first- to- file " system. Under a " first- to- file " system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. The America Invents Act includes a number of other significant changes to U. S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art and establish a new post- grant review system. The effects of these changes are currently unclear as the USPTO only recently developed new regulations and procedures in connection with the America Invents Act and many of the substantive changes to patent law, including the " first- to- file " provisions, only became effective in March 2013. In addition, the courts have yet to address many of these provisions and the applicability of the act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition. The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example: • others may be able to make or use compounds that are similar to the compositions of our product candidates but that are not covered by the claims of our patents or those of our licensors; • we or our licensors, as the case may be, may fail to meet our obligations to the U. S. government in regards to any in- licensed patents and patent applications funded by U. S. government grants, leading to the loss of patent rights; • we or our licensors, as the case may be, might not have been the first to file patent applications for these inventions; • others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights; • it is possible that our pending patent applications will not result in issued patents; • it is possible that there are prior public disclosures that could invalidate our or our licensors' patents, as the case may be, or parts of our or their patents; • it is possible that others may circumvent our owned or in- licensed patents; • it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our products or technology similar to ours; • the laws of foreign countries may not protect our or our licensors', as the case may be, proprietary rights to the same extent as the laws of the United States; • the claims of our owned or in- licensed issued patents or patent applications, if and when issued, may not cover our product candidates; • our owned or in- licensed issued patents may not provide us with any competitive advantages, may be narrowed in scope, or may be held invalid or unenforceable as a result of legal challenges by third parties; • the inventors of our owned or in- licensed patents or patent applications may become involved with competitors, develop products or processes which design around our patents or become hostile to us or the patents or patent applications on which they are named as inventors; • it is possible that our owned or in- licensed patents or patent applications omit individual (s) that should be listed as inventor (s) or include individual (s) that should not be listed as inventor (s), which may cause these patents or patents issuing from these patent applications to be held invalid or unenforceable; • we have engaged in scientific collaborations in the past, and are likely to continue to do so in the future. Such collaborators may develop adjacent or competing products to ours that are outside the scope of our patents; • we may not develop additional proprietary technologies for which we can obtain patent protection; • it is possible that product candidates or diagnostic tests that we develop may be covered by third parties' patents or other exclusive rights; or • the patents of others may have an adverse effect on our business. Risks Related to License and Collaboration Agreements We have entered into, and may enter into, license or other collaboration agreements that impose certain obligations on us. If we fail to comply with our obligations under such agreements with third parties or otherwise experience disruptions to our business relationships with our current or future licensors, we could lose rights that may be important to our business. In connection with our efforts to expand our pipeline of product candidates, we have entered into and may further enter into certain licenses or other collaboration agreements in the future pertaining to the in- license of rights to additional candidates. Such agreements may impose various reporting, diligence, milestone payment, royalty, insurance or other obligations on us. If we fail to comply with these obligations, our licensor or collaboration partners may have the right to terminate the relevant agreement, in which event we would not be able to develop or market the products covered by such licensed intellectual property, or to pursue other remedies. We may not be able to obtain licenses at a reasonable cost or on reasonable terms, if at all. Furthermore, if we lose intellectual property rights licensed under existing agreements or fail to obtain future licenses, we may be required to expend considerable time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected proprietary technologies and product candidates, which could harm our business significantly. Third- party patents may exist which might be enforced against our current or future proprietary technologies and product candidates, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and / or other forms of compensation to third parties Moreover, disputes may arise regarding intellectual property subject to a licensing agreement, including: • the scope of rights granted under the license agreement and other interpretation- related issues; • the extent to which our product candidates, technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; • the sublicensing of patent and other rights under our collaborative development relationships; • our diligence obligations under the license agreement and what activities satisfy those diligence obligations; • the inventorship and ownership of inventions and know- how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and • the priority of invention of patented technology. In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or could increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations and prospects. In addition, we may have limited control over the maintenance and prosecution of these in- licensed patents and patent applications, or any other intellectual property that may be related to our in- licensed intellectual property. For example, we cannot be certain that such activities by any future licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents and other intellectual property rights. If any of our current or future licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business and our competitors could market competing products using the intellectual property. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners, including loss of our right to prosecute the licensed patent applications or early termination of the license by our licensor. We also may have limited control over the manner in which our licensors initiate an infringement proceeding against a third- party infringer of the intellectual property rights, or defend certain of the intellectual property that is licensed to us. It is possible that the licensors' infringement proceeding or defense activities may be less vigorous than had we conducted them ourselves. Our technology licensed from third parties may be subject to retained rights. Any license we may enter into could provide for the retention by the licensor of certain rights under their agreements with us, including for example, the right to use the underlying technology for noncommercial academic and research use, to publish general scientific findings from research related to the technology, and to make customary scientific and scholarly disclosures of information relating to the technology. It is difficult to monitor whether any future licensors will limit their use of the technology to these uses, and we may incur substantial expenses to enforce our rights to our licensed technology in the event of misuse. In addition, the U. S. government retains certain rights in inventions produced with its financial assistance under the Patent and Trademark Law Amendments Act, or the Bayh- Dole Act. The U. S. government retains a " nonexclusive, nontransferable, irrevocable, paid- up license " for its own benefit. The Bayh- Dole Act also provides federal agencies with " march- in rights. " March- in rights allow the government, in specified circumstances, to require the contractor or successors in title to the patent to grant a " nonexclusive, partially exclusive, or exclusive license " to a " responsible applicant or applicants. " If the patent owner refuses to do so, the government may grant the license itself. The Bayh- Dole Act also imposes other obligations, including the requirement that products covered by the government funded patents be manufactured in the United States. We sometimes collaborate with academic institutions to accelerate our preclinical research or development. In the future, we may own or license technology which is critical to our business that is developed in whole or in part with federal funds subject to the Bayh- Dole Act. If the federal government exercises its rights under the Bayh- Dole Act, our ability to enforce or otherwise exploit patents covering such technology may be adversely affected. We may rely on trade secrets and proprietary know- how, which can be difficult to trace and enforce and, if we are unable to protect the confidentiality of our trade secrets and proprietary know- how, our business and competitive position would be harmed. In addition to patent protection, we rely heavily upon know- how and trade secret protection, as well as non- disclosure agreements and invention assignment agreements with our employees, consultants and third parties, to protect our confidential and proprietary information, especially where we do not believe patent protection is appropriate or obtainable. In addition to contractual measures, we try to protect the confidential nature of our proprietary information using physical and technological security measures. Such measures may not, for example, in the case of misappropriation of a trade secret by an employee or third- party with authorized access, provide adequate protection for our proprietary information. Our security measures may not prevent an employee or consultant from misappropriating our trade secrets and providing them to a competitor, and recourse we take against such misconduct may not provide an adequate remedy to protect our interests fully. Additionally, because we expect to rely on third parties in the development and manufacture of our product candidates, we must, at times, share trade secrets with them. Any disclosure, either intentional or unintentional, by our employees, the employees of third parties with whom we share our facilities or third- party consultants and vendors that we engage to perform research, clinical trials or manufacturing activities, or misappropriation by third parties (such as through a cybersecurity breach) of our trade secrets or proprietary information could enable competitors to duplicate or surpass our technological achievements. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret can be difficult, expensive, and time- consuming, and the outcome is unpredictable. In addition, trade secrets may be independently developed by others in a manner that could prevent legal recourse by us. If any of our confidential or proprietary information, such as our trade secrets, were to be disclosed or misappropriated, or if any such information was independently developed by a competitor, our competitive position could be harmed. In addition, courts outside the United States are sometimes less willing to protect trade secrets. If we choose to go to court to stop a third- party from using any of our trade secrets, we may incur substantial costs. These lawsuits may consume our time and other resources even if we are successful. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Risks Related to Potential Third- Party Claims Third- party claims of intellectual property infringement may prevent or delay our product discovery and development efforts. Our commercial success depends in part on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and biopharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation, inter partes review, post grant review, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our product candidates and / or proprietary technologies infringe their intellectual property rights. Numerous U. S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing our product candidates. As the biotechnology and biopharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others. Moreover, it is not always clear to industry participants, including us, which patents cover various types of drugs, products or their methods of use or manufacture. Thus, because of the large number of patents issued and patent applications filed in our fields, there may be a risk that third parties may allege they have patent rights encompassing our product candidates, technologies or methods. We also may be subject to, or threatened with, other third - party claims relating to alleged infringement of intellectual property or other proprietary rights, including breach of nondisclosure, nonuse, noncompetition and non- solicitation provisions, intellectual property assignment and ownership, and misuse or misappropriation of intellectual property, trade secrets and other confidential information, among others. If a court of competent jurisdiction finds us liable for any such claims, we may be prohibited from using certain intellectual property, trade secrets and confidential information, effectively blocking our ability to seek patent protection for our inventions and slowing or halting the progress of our clinical development and commercialization efforts. If a third- party claims that we infringe its intellectual property rights, we may face a number of issues, including, but not limited to: • infringement and other intellectual property claims , which, regardless of merit, may be expensive and time- consuming to litigate and may divert our management' s attention from our core business; • substantial damages for infringement, which we may have to pay if a court decides that the product candidate or technology at issue infringes on or violates the third- party' s rights, and, if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner' s attorneys' fees; • a court prohibiting us from developing, manufacturing, marketing or selling our product candidates, or from using our proprietary technologies, unless the third- party licenses its product rights to us, which it is not required to do; • if a license is available from a third- party, we may have to pay substantial royalties, upfront fees and other amounts, and / or grant cross- licenses to intellectual property rights for our products and any license that is available may be non- exclusive, which could result in our competitors gaining access to the same intellectual property; and • redesigning our product candidates or processes so that they do not infringe, which may not be possible or may require substantial monetary expenditures and time. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations or could otherwise have a material adverse effect on our business, results of operations, financial condition and prospects. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. If we are found to infringe a third- party' s intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing technologies, product candidates or products. Alternatively, we may be required to obtain a license from such third- party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing technologies, product candidates or products. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non- exclusive, thereby giving our competitors access to the same technologies licensed to us. A finding of infringement could prevent us from commercializing our technologies, product candidates or products or force us to cease some of our business operations, and could divert the time and attention of our technical personnel and management, cause development delays, and / or require us to develop non- infringing technology, which may not be possible on a cost- effective basis, any of which could materially harm our business. In the event of a successful claim of infringement against us, we may have to pay substantial monetary damages, including treble damages and attorneys' fees for willful infringement, pay royalties and other fees, redesign our infringing drug or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Our collaborators may assert ownership or commercial rights to inventions they develop from research we support or that we develop or otherwise arising from the collaboration. We collaborate with ~~several~~ **various** institutions, universities, medical centers, physicians and researchers in scientific matters and expect to continue to enter into additional collaboration agreements. In certain cases, we do not have written agreements with these collaborators, or the written agreements we have do not cover intellectual property rights. Also, we rely on numerous third parties to provide us with materials that we use to conduct our research activities and develop our product candidates. If we cannot successfully negotiate sufficient ownership and commercial rights to any inventions that result from our use of a third- party collaborator' s materials, or if disputes arise with respect to the intellectual property developed with the use of a collaborator' s samples, or data developed in a collaborator' s study, in cases where written agreements either do or do not exist, we may be limited in our ability to capitalize on the market potential of these inventions or developments. Additionally, our licensors may have relied on third- party consultants or collaborators or on funds from third parties, such as the U. S. government, such that our licensors are not the sole and exclusive owners of the patents we in- license. If other third parties have ownership rights or other rights to our in- licensed patents, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects. We may become subject to claims challenging the inventorship or ownership of our patents and other intellectual property. We may be subject to claims that employees, former employees or third parties have an interest in our patents or other intellectual property as an inventor or co- inventor. The failure to name the proper inventors on a patent application can result in the patents issuing thereon being unenforceable. Inventorship disputes may arise from conflicting views regarding the contributions of different individuals named as inventors or not named as inventors, the effects of foreign laws where foreign nationals are involved in the development of the subject matter of the patent, conflicting obligations of third parties involved in developing our product candidates or as a result of questions regarding co- ownership of potential joint inventions. Litigation may be necessary to resolve these and other claims challenging inventorship and / or ownership. Alternatively, or additionally, we may enter into agreements to clarify the scope of our rights in such intellectual property. If we fail in defending any such claims, or portion of such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. In addition, while we require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self- executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects. Third parties may assert that we are employing their proprietary technology without authorization. There may be third- party patents of which we are currently unaware with claims to compounds, compositions of matter, materials, formulations, methods of manufacture or methods of use that encompass the composition, use or manufacture of our product candidates. There may be currently pending patent applications of which we are currently unaware which may later result in issued patents that our product candidates or their use or manufacture may infringe. It is also possible that patents owned by third parties of which we are aware, but which we do not believe are relevant to our product candidates and other proprietary technologies we may develop, could be found to be infringed by our product candidates. If any third- party patent were held by a court of competent jurisdiction to cover our product candidates, intermediates used in the manufacture of our product candidates or our materials generally, aspects of our formulations or methods of use, the holders of any such patent may be able to block our ability to develop and commercialize the product candidate unless we obtained a license or until such patent expires or is finally determined to be held invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third- party patent on commercially reasonable terms, or at all, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business. Even if we obtain a license, it may be non- exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible, or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly. Third parties may assert that our employees or consultants have wrongfully used or disclosed confidential information or misappropriated trade secrets. As is common in the biotechnology and biopharmaceutical industries, we employ individuals who were previously employed at universities or other biotechnology or biopharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees and consultants 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 our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third parties. 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. A court could also prohibit us from using technologies or features that are essential to our product candidates, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. Even if we are successful in defending against such claims, 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. This type of litigation or proceeding could substantially increase our operating losses and reduce our resources available for development 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 substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other intellectual property related proceedings could adversely affect our ability to compete in the marketplace. We may not be successful in obtaining or maintaining necessary rights to develop any future product candidates on acceptable terms. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in- license or use these proprietary rights. Our product candidates may also require specific formulations to work effectively and efficiently **,** and these rights may be held by others. We may develop products containing our compounds and pre- existing biopharmaceutical compounds. We may be unable to acquire or in- license any compounds, compositions, formulations, methods of use, processes or other third- party intellectual property rights from third parties that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compounds, compositions formulations, methods of use or processes covered by such third- party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license, it may be non- exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology. Additionally, we sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions may provide us with an option to negotiate a license to any of the institution' s rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third- party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer. The licensing and acquisition of third- party intellectual property rights is a competitive area, and companies, which may be more established, or have different or greater resources than we do, may also be pursuing strategies to license or acquire third- party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire. We may be involved in lawsuits to protect or enforce our patents or other intellectual property, or the patents or intellectual property of our licensors, which could be expensive, time- consuming and unsuccessful. Competitors or other third parties may infringe our patents, trademarks, copyrights or other intellectual property, or the intellectual property of our current or future licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time- consuming and divert time and attention of our management and scientific personnel. Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In addition, in any infringement proceeding, a court may decide that one or more of our patents is not valid or is unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question or for other reasons. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly, and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. We may choose to challenge the patentability of claims in a third- party' s U. S. patent by requesting that the USPTO review the patent claims in an ex- parte re- examination, inter partes review or post- grant review proceedings. These proceedings are expensive and may consume our time or other resources. We may choose to challenge a third- party' s patent in patent opposition proceedings in the European Patent Office, or EPO, or other foreign patent office. The costs of these opposition proceedings could be substantial, and may consume our time or other resources. If we fail to obtain a favorable result at the USPTO, EPO or other patent office then we may be exposed to litigation by a third- party alleging that the patent may be infringed by our product candidates or proprietary technologies. In addition, because some patent applications in the United States may be maintained in secrecy until the patents are issued, patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing or, in some cases, not at all, and publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications for technology covered by our owned and in- licensed issued patents or our pending applications, or that we or, if applicable, a licensor were the first to invent the technology. Our competitors may have filed, and may in the future file, patent applications covering our products or technology similar to ours. Any such patent application may have priority over our owned and in- licensed patent applications or patents, which could require us to obtain rights to issued patents covering such technologies. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. If another party has filed a U. S. patent application on inventions similar to those owned by or in- licensed to us, we or, in the case of in- licensed technology, the licensor may have to participate in an interference or derivation proceeding declared by the USPTO to determine priority of invention in the United States. If we or one of our licensors is a party to an interference or derivation proceeding involving a U. S. patent application on inventions owned by or in- licensed to us, we may incur substantial costs, divert management' s time and expend other resources, even if we are successful. Interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms or at all, or if a non- exclusive license is offered and our competitors gain access to the same technology. Litigation or interference proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States. Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. 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 litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock. Moreover, we may not have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. 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. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. 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. Risks Related to Patent Laws and Protection Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non- compliance with these requirements. Periodic maintenance fees, renewal fees, annuities fees and various other governmental fees on any issued patent and / or patent application are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent and / or patent application. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent application process and following the issuance of a patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non- payment of fees and failure to properly legalize and submit formal documents. In certain circumstances, even inadvertent noncompliance events may permanently and irrevocably jeopardize patent rights. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business. Any patents, if issued, covering our product candidates could be found invalid or unenforceable if challenged in court or the USPTO. If we or one of our licensors initiate legal proceedings against a third- party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate, as applicable, is invalid and / or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and / or unenforceability are commonplace, and there are numerous grounds upon which a third- party can assert invalidity or unenforceability of a patent. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non- enablement or insufficient written description. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during patent prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent' s claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention, or decide that the other party' s use of our patented technology falls under the safe harbor to patent infringement under 35 U. S. C. § 271 (e) (1). An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive position, business, financial conditions, and prospects. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re- examination, inter partes review, post grant review, and equivalent proceedings in foreign jurisdictions (e. g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and / or unenforceability, or if we are otherwise unable to adequately protect our rights, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and product candidates. Likewise, our current licensed or owned patents are expected to expire between 2029 and ~~2041~~ **2043**, without taking into account any possible patent term adjustments or extensions. Our earliest patents may expire before, or soon after, our first product achieves marketing approval in the United States or foreign jurisdictions. Upon the expiration of our current patents, we may lose the right to exclude others from practicing these inventions. The expiration of these patents could also have a similar material adverse effect on our business, results of operations, financial condition and prospects. Our current licensed or owned pending patent applications covering our proprietary technologies or our product candidates that if issued as patents are expected to expire from 2029 through 2043, without taking into account any possible patent term adjustments or extensions. However, we cannot be assured that the USPTO or relevant foreign patent offices will grant any of these patent applications not already granted or that a court will uphold any patents already issued. Changes in patent law in the United States and in foreign jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products. Our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Assuming that other requirements for patentability are met, prior to March 16, 2013, in the United States, the first to invent 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. On March 16, 2013, under the America Invents Act, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. A third party that files a patent application in the USPTO on or after March 16, 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either (i) file any patent application related to our product candidates or (ii) invent any of the inventions claimed in our or our licensor' s patents or patent applications. The America Invents Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post- grant proceedings, including post- grant review, inter- parties review and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Therefore, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or in- licensed patent applications and the enforcement or defense of our owned or in- licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. In addition, the patent positions of companies in the development and commercialization of biopharmaceuticals are particularly uncertain. Recent U. S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U. S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future. **Further, on June 1, 2023, the European Union Patent Package, or the EU Patent Package, regulations were implemented with the goal of providing a single pan- European Unitary Patent and a new European Unified Patent Court, or UPC, for litigation involving European patents. As a result, all European patents, including those issued prior to ratification of the EU Patent Package, now by default automatically fall under the jurisdiction of the UPC. It is uncertain how the UPC will impact granted European patents in the biotechnology and pharmaceutical industries. Our European patent applications, if issued, could be challenged in the UPC. During the first seven years of the UPC' s existence, the UPC legislation allows a patent owner to opt its European patents out of the jurisdiction of the UPC. We may decide to opt out our future European patents from the UPC, but doing so may preclude us from realizing the benefits of the UPC. Moreover, if we do not meet all of the formalities and requirements for opt- out under the UPC, our future European could remain under the jurisdiction of the UPC. The UPC will provide our competitors with a new forum to centrally revoke our European patents, and allow for the possibility of a competitor to obtain pan- European injunction. Such a loss of patent protection could have a material adverse impact on our business and our ability to commercialize our technology and product candidates and, resultantly, on our business, financial condition, prospects and results of operations.** We have limited foreign intellectual property rights and may not be able to protect our intellectual property rights throughout the world. We have limited intellectual property rights outside the United States. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of, and may require a compulsory license to, patents, trade secrets and other intellectual property protection, particularly those relating to biopharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products against third parties in violation of our proprietary rights generally. The initiation of proceedings by third parties to challenge the scope or validity of our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate **,** and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license **. In addition, geo- political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors. For example, the United States and foreign government actions related to Russia' s conflict in Ukraine may limit or prevent filing, prosecution, and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees from the United States without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our**

inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected . Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time. Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U. S. non-provisional filing date. Various extensions such as patent term adjustments and / or extensions, may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive technologies and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. If we do not obtain patent term extension and data exclusivity for any product candidates we may develop, our business may be materially harmed. Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U. S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Action of 1984, or the Hatch- Waxman Amendments. The Hatch- Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration and may take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data to launch their product earlier than might otherwise be the case. If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected. Our current or future trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive rejections of our applications by the USPTO or in other foreign jurisdictions. We may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks **that may be costly and time- consuming** , and our trademarks may not survive such proceedings. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected. We may license our trademarks and trade names to third parties, such as distributors. Though these license agreements may provide guidelines for how our trademarks and trade names may be used, a breach of these agreements or misuse of our trademarks and tradenames by our licensees may jeopardize our rights in or diminish the goodwill associated with our trademarks and tradenames. Risks Related to Our Dependence on Third Parties Risks Related to Third Parties Generally We rely on third parties to assist in conducting our preclinical studies and clinical trials. If they do not perform satisfactorily, we may not be able to obtain regulatory approval or commercialize our product candidates, or such approval or commercialization may be delayed, and our business could be substantially harmed. We have relied upon and plan to continue to rely on third parties, such as laboratories, CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our preclinical studies and clinical trials and expect to rely on these third parties to conduct preclinical studies and clinical trials of any other product candidate that we develop. Any of these third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. Moreover, delays may occur, which could negatively impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects. Although our reliance on these third parties for preclinical and clinical development activities limits our control over these activities, we remain responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards. Moreover, human clinical research must comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites and IRBs. If we or our third- party contractors fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the regulatory authorities may require us to perform additional clinical trials before approving our product candidates, which would delay the regulatory approval process. We cannot be certain that, upon inspection, a regulatory authority will determine that any of our clinical trials comply with GCPs. The third parties conducting clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time, skill and resources to our ongoing development programs. These outside contractors may not assign as great a priority to our programs or pursue them as diligently as we would if we were undertaking such programs ourselves. These contractors may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities, which could impede their ability to devote appropriate time to our clinical programs. If these third parties, including clinical investigators, do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we may not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. In such an event, our financial results and the commercial prospects for any product candidates that we seek to develop could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed. If our relationships with any third parties conducting our studies are terminated, we may be unable to enter into arrangements with alternative third parties on commercially reasonable terms, or at all. Switching or adding third parties to conduct our studies involves substantial cost and requires extensive management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays occur, which can materially impact our ability to meet our desired preclinical and clinical development timelines. Although we carefully manage our relationships with third parties conducting our studies, we cannot assure that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material and adverse effect on our business, financial condition and results of operations. We also 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 regulatory approval of our product candidates or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue. Risks Related to Third- Party Manufacturers We contract with third parties for the manufacture of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or drugs or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts. We do not currently have the infrastructure or internal capability to manufacture supplies of our product candidates for use in development and commercialization. We rely, and expect to continue to rely, on third- party manufacturers for the production of our product candidates for preclinical studies and clinical trials under the guidance of members of our organization. If we were to experience an unexpected loss of supply of any of our product candidates or any of our future product candidates for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing clinical trials. We expect to continue to rely on third- party manufacturers for the commercial supply of any of our product candidates for which we obtain marketing approval. We may be unable to maintain or establish required agreements with third- party manufacturers 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: • the failure of the third party to manufacture our product candidates according to our schedule, or at all, including if our third- party contractors give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreements between us and them; • the reduction or termination of production or deliveries by suppliers, or the raising of prices or renegotiation of terms; • the termination or nonrenewal of arrangements or agreements by our third- party contractors at a time that is costly or inconvenient for us; • the breach by the third- party contractors of our agreements with them; • the failure of third- party contractors to comply with applicable regulatory requirements; • the failure of the third party to manufacture our product candidates according to our specifications; • the mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or study drug or placebo not being properly identified; • clinical supplies not being delivered to clinical sites on time and at expected cost due to inflationary impacts, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and • the misappropriation of our proprietary information, including our trade secrets and know- how. We do not have complete control over all aspects of the manufacturing process of, and are dependent on, our contract manufacturing partners for compliance with cGMP or similar regulations for manufacturing both active drug substances and finished drug products. Third- party manufacturers may not be able to comply with cGMP or similar regulations or similar regulatory requirements outside of the United States. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and / or maintain marketing approval for their manufacturing facilities. In addition, we do not have control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain marketing approval for or market our product candidates, if approved. Our failure, or the failure of our third- party manufacturers, to comply with applicable regulations 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 drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates or drugs and harm our business and results of operations. Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis. If any third- party manufacturer of our product candidates is unable to increase the scale of its production of our product candidates, and / or increase the product yield of its manufacturing, then our costs to manufacture the product may increase and commercialization may be delayed. In order to produce sufficient quantities to meet the demand for clinical trials and, if approved, subsequent commercialization of our product candidates that we may develop, our third- party manufacturers will be required to increase their production and optimize their manufacturing processes while maintaining the quality of the product. The transition to larger scale production could prove difficult. In addition, if our third party manufacturers are not able to optimize their manufacturing processes to increase the product yield for our product candidates, or if they are unable to produce increased amounts of our product candidates while maintaining the quality of the product, then we may not be able to meet the demands of clinical trials or market demands, which could decrease our ability to generate profits and have a material adverse impact on our business and results of operation. Risks Related to Third- Party Suppliers We depend on third- party suppliers for key raw materials used in our manufacturing processes, some of which are our sole source of supply, and the loss of these third- party suppliers or their inability to supply us with adequate raw materials could harm our business. We rely on our CDMOs to purchase from third- party suppliers the materials necessary to produce our product candidates for our clinical trials. We do not have, nor do we expect to enter into, any agreements for the commercial production of these raw materials, and we do not expect to have any control over the process or timing of our CDMOs' acquisition of raw materials needed to produce our product candidates. Any significant delay in the supply of a product candidate or the raw material components thereof for an ongoing clinical trial due to a manufacturer' s need to replace a third- party supplier of raw materials could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates. Additionally, if our future manufacturers or we are unable to purchase these raw materials to commercially produce any of our product candidates that gains regulatory approvals, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates. Furthermore, for those third- party suppliers who may be our sole source of supply of certain materials, we may not have arrangements in place for a redundant or second- source supply of any such materials in the event any of our current suppliers cease their operations for any reason. Establishing additional or replacement suppliers for the raw materials used in our product candidates, if required, may not be accomplished quickly. If we are able to find a replacement supplier, such replacement supplier would need to be qualified and may require additional regulatory inspection or approval, which could result in further delay. We depend on collaborations with third parties for the research, development and commercialization of certain of the product candidates we may develop. If any such collaborations are not successful, we may not be able to realize the market potential of those product candidates. We have, and may seek in the future, third- party collaborators for the research, development and commercialization of certain of the product candidates we may develop. For example, we have a collaboration with Ionis Pharmaceuticals, Inc. to further our development of product candidates and to enhance our research efforts directed to developing a product candidate for the treatment of epilepsy. Our likely collaborators for any other collaboration arrangements include large and mid- size pharmaceutical companies, regional and national pharmaceutical companies, biotechnology companies and academic institutions, such as The Florey Institute of Neuroscience. If we enter into any such arrangements with any third parties, we will likely have shared or limited control over the amount and timing of resources that our collaborators dedicate to the development or potential commercialization of any product candidates we may seek to develop with them. Our ability to generate revenue from these arrangements with commercial entities will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any collaboration that we enter into. Collaborations involving our research programs, or any product candidates we may develop, pose the following risks to us: • collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations; • collaborators may not properly obtain, maintain, enforce or defend intellectual property or proprietary rights relating to our product candidates or research programs, or may use our proprietary information in such a way as to expose us to potential litigation or other intellectual property related proceedings, including proceedings challenging the scope, ownership, validity and enforceability of our intellectual property; • collaborators may own or co- own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property or such product candidates or research programs; • we may need the cooperation of our collaborators to enforce or defend any intellectual property we contribute to or that arises out of our collaborations, which may not be provided to us; • collaborators may control certain interactions with regulatory authorities, which may impact our ability to obtain and maintain regulatory approval of our products candidates; • disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our product candidates or research programs or that result in costly litigation or arbitration that diverts management attention and resources; • collaborators may decide to not pursue development and commercialization of any product candidates we develop 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; • collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates or research programs if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; • collaborators may restrict us from researching, developing or commercializing certain products or technologies without their involvement; • collaborators with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidates; • we may lose certain valuable rights under circumstances identified in our collaborations, including if we undergo a change of control; • collaborators may grant sublicenses to our technology or product candidates or undergo a change of control and the sublicensees or new owners may decide to take the collaboration in a direction which is not in our best interest; • collaborators may become bankrupt, which may significantly delay our research or development programs, or may cause us to lose access to valuable technology, know- how or intellectual property of the collaborator relating to our products, product candidates or research programs; • key personnel at our collaborators may leave, which could negatively impact our ability to productively work with our collaborators; • collaborations may require us to incur short and long- term expenditures, issue securities that dilute our stockholders or disrupt our management and business; • if our collaborators do not satisfy their obligations under our agreements with them, or if they terminate our collaborations with them, we may not be able to develop or commercialize product candidates as planned; •

collaborations may require us to share in development and commercialization costs pursuant to budgets that we do not fully control and our failure to share in such costs could have a detrimental impact on the collaboration or our ability to share in revenue generated under the collaboration; • collaborations may be terminated in their entirety or with respect to certain product candidates or technologies and, if so terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates or technologies; and • collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our development or commercialization program under such collaboration could be delayed, diminished or terminated. We may face significant competition in seeking appropriate collaborations. Recent business combinations among biotechnology and pharmaceutical companies have resulted in a reduced number of potential collaborators. In addition, the negotiation process is time- consuming and complex, and we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop product candidates or bring them to market and generate product revenue. If we enter into collaborations to develop and potentially commercialize any product candidates, we may not be able to realize the benefit of such transactions if we or our collaborator elects not to exercise the rights granted under the agreement or if we or our collaborator are unable to successfully integrate a product candidate into existing operations and company culture. The failure to develop and commercialize a product candidate pursuant to our agreements with our current or future collaborators could prevent us from receiving future payments under such agreements, which could negatively impact our revenues. In addition, if our agreement with any of our collaborators terminates, our access to technology and intellectual property licensed to us by that collaborator may be restricted or terminate entirely, which may delay our continued development of our product candidates utilizing the collaborator’ s technology or intellectual property or require us to stop development of those product candidates completely. We may also find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. Many of the risks relating to product development, regulatory approval, and commercialization described in this “ Risk Factors ” section also apply to the activities of our collaborators and any negative impact on our collaborators may adversely affect us. We may acquire businesses or products, or form strategic alliances, in the future, and we may not realize the benefits of such acquisitions or alliances. We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure that, following any such acquisition, we will achieve the expected synergies to justify the transaction. Risks Related to Employee Matters, Managing Our Business and Operations Risks Related to Business Operations Our business is subject to economic, political, regulatory and other risks associated with international operations. Our business is subject to risks associated with conducting business internationally. Some of our suppliers and collaborative relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including: • economic weakness, including inflation, or political instability in particular non- U. S. economies and markets; • differing and changing regulatory requirements in non- U. S. countries; • challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States, including our ability to prosecute or maintain patents in Russia due to the sanctions imposed by the United States and other countries on Russia as a result of Russia’ s invasion of Ukraine and our ability to enforce patents due to Russia' s March 2022 decree that allows the use of inventions, utility models and industrial designs that are held by intellectual property owners from" unfriendly countries," including the United States, without the consent of or payment of any compensation to such owners; • difficulties in compliance with non- U. S. laws and regulations; • changes in non- U. S. regulations and customs, tariffs and trade barriers; • changes in non- U. S. currency exchange rates and currency controls; • changes in a specific country’ s or region’ s political or economic environment; • trade protection measures, import or export licensing requirements or other restrictive actions by U. S. or non- U. S. governments; • negative consequences from changes in tax laws; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • workforce uncertainty in countries where labor unrest is more common than in the United States; • difficulties associated with staffing and managing international operations, including differing labor relations • potential liability under the Foreign Corrupt Practices Act, U. K. Bribery Act of 2010 or comparable foreign laws, including expanded sanctions imposed by the United States and other countries on Russia due to Russia' s invasion of Ukraine; • business interruptions resulting from geo- political actions, including war and terrorism, such as Russia' s invasion of Ukraine, natural disasters including earthquakes, typhoons, floods and fires, or health epidemics such as COVID- 19; and • cyberattacks, which are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect, including an increased likelihood that Russia' s invasion of Ukraine could result in more cyberattacks or cybersecurity incidents. These and other risks associated with our planned international operations may materially adversely affect our ability to attain profitable operations. We or the third parties upon whom we depend may be adversely affected by natural disasters, health epidemics or other business interruptions and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster. Natural disasters or health epidemics could severely disrupt our operations, and have a material adverse impact on our business, results of operations, financial condition, and prospects. If a natural disaster, power outage, health epidemic or other event occurred that prevented us from conducting our clinical trials, releasing clinical trial results or delaying our ability to obtain regulatory approval for our product candidates, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. For example, since December 2019, several novel strains of coronavirus have been identified and continue to spread globally, including in the United States, and the disease they cause, COVID- 19, has been declared a pandemic by the World Health Organization. The COVID- 19 pandemic and government measures taken in response thereto have impacted the global economy and may impact our operations, including the potential interruption of our clinical trial activities, regulatory reviews and our supply chain. As a result of stringent COVID- 19 lockdown restrictions, we had previously observed delays in trial enrollment for our Phase 2a trial for ulixacaltamide in Australia. While these lockdowns did not lead to a material impact on our business, we cannot predict the scope and severity of potential shutdowns or disruptions of businesses due to COVID- 19 or another pandemic, epidemic or outbreak of an infectious disease in the future. At present, we are not experiencing significant impact or delays from the COVID- 19 pandemic on our business, operations and, if our product candidates are approved, commercialization plans. We continue to closely monitor the COVID- 19 pandemic as we evolve our clinical development plans. The extent to which the COVID- 19 pandemic impacts our business will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of the novel coronavirus strains, and of any future- identified novel coronavirus strains, the effectiveness of actions taken in the United States and other countries to contain the coronavirus strains or treat their impact, including the adoption and effectiveness of vaccines and vaccine distribution efforts and the extent and duration of the pandemic' s impact on economic conditions and social activity, including with respect to inflationary pressures and supply chain shortages and disruptions, among others. Risks Related to Employees We depend heavily on our executive officers, principal consultants and others, and the loss of their services would materially harm our business. Our success depends, and will likely continue to depend, upon our ability to retain the services of our current executive officers, principal consultants and others, including Marcio Souza, our President and Chief Executive Officer, and Timothy Kelly, our Chief Financial Officer. We have entered into employment agreements with Mr. Souza and Mr. Kelly, but they may terminate their employment with us at any time. The loss of their services might impede the achievement of our research, development and commercialization objectives. ~~In August 2022, Bernard Ravina stepped down as our Chief Medical Officer and transitioned to a part- time role as strategic advisor. This change in our senior management may be disruptive to our business, and if we are unable to manage an orderly transition of Dr. Ravina' s duties to our clinical team or to a new Chief Medical Officer, our business may be adversely affected.~~ We do not maintain " key person " insurance for any of our executives or other employees. Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. Our industry has experienced significant demand for, and a high rate of turnover of, management personnel in recent years. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key employees on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we have a limited number of employees to manage and operate our business. We cannot ensure that we will be able to maintain adequate staff to develop our product candidates, to run our operations or accomplish our objectives. If we are unable to maintain adequate staffing levels, our business and operations could be materially adversely affected. We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategies. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited. Our employees, independent contractors, consultants, collaborators and contract research organizations may engage in misconduct or other improper activities, including non- compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation. We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and / or negligent conduct or disclosure of unauthorized activities to us that violates: • regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities; • manufacturing standards; • federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non- U. S. regulatory authorities; and • laws that require the accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of product materials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this kind of 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, standards or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. 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 civil, criminal and administrative penalties, damages, monetary fines, disgorgement, integrity oversight and reporting obligations, possible exclusion from participation in the United States in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations. We expect to expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of regulatory affairs and sales, marketing and distribution, as well as to support our public company operations. To manage these growth activities, we must continue to implement and improve our managerial, operational, quality and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion or relocation of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion or relocation of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates. Risks Related to Data Privacy and Cybersecurity Cyberattacks or other failures in our telecommunications or information technology systems, or those of our collaborators, contract research organizations, third- party logistics providers, distributors or other contractors or consultants, could result in information theft, data corruption and significant disruption of our business operations. We, our collaborators, our CROs, third- party logistics providers, distributors and other contractors and consultants utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, **our IT systems and those of such third parties, are increasingly vulnerable to attack, damage and interruption from natural disasters, terrorism, war, telecommunication and electrical failures, hacking,** cyber incidents, including third parties gaining access to employee accounts using stolen or inferred credentials, ~~computer~~ **malicious code,** malware, viruses **(e. g., ransomware)** , spamming, phishing attacks ~~or~~ **and** other ~~means~~ **social engineering schemes** , **employee theft or misuse, human error, fraud, denial or degradation of service attacks,** and **sophisticated nation- state and nation- state- supported actors or other** deliberate attacks and attempts to gain unauthorized access to ~~computer~~ **IT** systems and networks, **as such attacks** have increased in frequency and sophistication. Attacks upon **IT** ~~information technology~~ systems are also increasing in their levels of persistence and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. **We** ~~As a result of the COVID-19 pandemic, we~~ may also face increased cybersecurity risks due to our reliance on internet technology and ~~the number of~~ our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. **Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence. We and certain of our service providers are from time to time subject to cyberattacks and security incidents.** While we do not believe that we have experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our **business operations and** drug development programs. These threats pose a risk to the security of our, our collaborators', our CROs', third- party logistics providers', distributors' and other contractors' and consultants' systems and networks, and the confidentiality, availability and integrity of our data. There can be no assurance that ~~we~~ **our cybersecurity risk management program and processes, including our policies, controls or procedures,** will be **fully implemented, complied with or** successful in preventing cyberattacks or ~~successfully~~ **other IT disruptions, or in** mitigating their effects. Similarly, there can be no assurance that our collaborators, CROs, third- party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems **. Further, the costs associated with the investigation, remediation and potential notification of a breach to counterparties and data subjects could be material** . Any cyberattack, data breach or destruction or loss of data could result in a violation of applicable U. S. and international privacy, data protection and other laws, and subject us to litigation and governmental investigations and proceedings by federal, state and local regulatory entities in the United States and by international regulatory entities, resulting in exposure to material civil and / or criminal liability. Further, our general liability insurance and corporate risk program may not cover all potential claims to which we are exposed and may not be adequate to indemnify us for all liability that may be imposed; and could have a material adverse effect on our business and prospects. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials for any of our product candidates could result in delays in our development and regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyberattacks or other data security breaches and may incur significant additional expense to implement further data protection measures. We rely on a set of cloud- based software services and access these services via the Internet for the vast majority of our computing, storage, bandwidth and other services. Any disruption of or interference with our use of our cloud- based services would negatively affect our operations and could seriously harm our business. We use several distributed computing infrastructure platforms for business operations, or what is commonly referred to as " cloud " computing services and we access these services via the Internet. Any transition of the cloud services currently provided by an existing vendor to another cloud provider would be difficult to implement and will cause us to incur significant time and expense. Given this, any significant disruption of or interference with our use of these cloud computing services would negatively impact our operations and our business would be seriously harmed. If our employees or partners are not able to access our cloud computing services or encounter difficulties in doing so, we may experience business disruption. The level of service provided by our cloud computing vendors, including the ability to secure our confidential information and the confidential information of third parties that is shared with us, may also impact the perception of our company and could seriously harm our business and reputation and create liability for us. If a cloud computing service that we use experiences interruptions in service regularly or for a prolonged basis, or other similar issues, our business could be seriously harmed. In addition, a cloud computing service may take actions beyond our control that could seriously harm our business, including: • discontinuing or limiting our access to its platform; • increasing pricing terms; • terminating or seeking to terminate our contractual relationship altogether; or • modifying or interpreting its terms of service or other policies in a manner that impacts our ability to run our business and operations. Our cloud computing services have broad discretion to change and interpret its terms of service and other policies with respect to us, and those actions may be unfavorable to us. Our cloud computing services may also alter how we are able to process data on the platform. If a cloud computing services makes changes or interpretations that are unfavorable to us, our business could be seriously harmed. Our efforts to protect the information shared with us may be unsuccessful due to the actions of third parties, software bugs or other technical malfunctions, employee error or malfeasance or other factors. In addition, third parties may attempt to fraudulently induce employees or users to disclose information to gain access to our data or third- party data entrusted to us. If any of these events occur, our or third- party information could be accessed or disclosed improperly. Some partners or collaborators may store information that we share with them on their own computing system. If these third parties fail to implement adequate data- security practices or fail to comply with our policies, our data may be improperly accessed or disclosed. And even if these third parties take all of these steps, their networks may still suffer a breach, which could compromise our data. Any incidents where our information is accessed without authorization, or is improperly used, or incidents that violate our policies, could damage our reputation and our brand and diminish our competitive position. In addition, affected parties or government authorities could initiate legal or regulatory action against us over those incidents, which could cause us to incur significant expense and liability or result in orders or consent decrees forcing us to modify our business practices. Concerns over our privacy practices, whether actual or unfounded, could damage our reputation and brand and deter users, advertisers and partners from using our products and services. Any of these occurrences could seriously harm our business. Risks Related to Tax Laws Legislation or other changes in ~~U. S.~~ tax law could adversely affect our business and financial condition. The legislation, regulations and rules regarding U. S. federal, state and local ~~income~~ **and non- U. S.** taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U. S. Treasury Department and by state and local **and non- U. S.** tax agencies. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many changes have been made to applicable tax laws and changes are likely to continue to occur in the future. ~~In particular, the U. S. federal government may enact significant changes to the taxation of business entities including, among others, an increase in the corporate income tax rate and the imposition of minimum taxes or surtaxes on certain types of income.~~ It cannot be predicted whether, when, in what form or with what effective dates ~~any~~ changes in tax laws, regulations or rules ~~,~~ promulgated or issued under existing or new tax laws ~~, which~~ **may take place. Any such changes** could result in an increase in our or our shareholders' tax liability or require changes in the manner in which we operate in order to minimize or mitigate any adverse effects of changes in tax law or in the interpretation thereof. If any such changes are enacted or implemented, we ~~eare~~ **are** currently unable to predict the ultimate impact on our business or holders of our common stock. Our ability to use our U. S. federal and state net operating loss carryforwards and certain other tax attributes may be limited. Our ability to use our U. S. federal and state net operating losses and tax credits is dependent upon our generation of future taxable income and income tax liabilities **. We** ~~, and we~~ cannot predict with certainty when, or whether, we will generate sufficient taxable income or income tax liabilities to use any or all of our net operating losses or tax credits. Our unused U. S. federal net operating losses generated in tax years beginning before January 1, 2018, and unused state net operating losses subject to expiration, will carry forward to offset future taxable income, if any, until such unused net operating losses expire. Our unused U. S. federal net operating losses generated in tax years beginning after December 31, 2017 will not expire and may be carried forward indefinitely, although, for taxable years beginning after December 31, 2020, ~~the deductibility of such~~ U. S. federal net operating losses ~~is limited~~ **may only be used** to **offset** 80 % of our taxable income in such taxable year. ~~In addition~~ **As a result** , ~~both our current and~~ **we may be required to pay U. S. federal income taxes in** future **years even if we generated net losses for U. S. federal income tax purposes in prior years. Although our U. S. federal and state tax credits generally will carry forward and be available to offset future income tax liabilities, certain of such tax credits may be subject to expiration. Accordingly, our U. S. federal and state** net operating losses and **tax credits subject to expiration could expire unused. In addition, both our current and future U. S. federal net operating losses and U. S. federal** tax credits may be subject to limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if we undergo an " ownership change, " generally defined as a greater than 50 percentage point change (by value) in ~~its~~ **our** equity ownership by certain stockholders or groups of stockholders over a rolling three- year period **. We have not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception, and our existing U. S. federal net operating losses and U. S. federal tax credits may be subject to limitations arising from previous ownership changes. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change. Our net operating losses and tax credits may be similarly limited under state law** . Risks Related to Our Common Stock Risks Related to Investment in Securities The price of our stock has been and may in the future be volatile, and you could lose all or part of your investment. The trading price of our common stock has been and is likely to continue to be highly volatile and has been subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. For example, the trading price of our common stock experienced a significant decline after our June 2022 announcement of the Phase 2 / 3 Aria Study results. In addition to the factors discussed in this " Risk Factors " section, factors that may affect the trading price of our common stock include: • the commencement, enrollment, completion or results of our current clinical trials of our product candidates; • any delay in identifying and advancing a clinical candidate for our other programs; • any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority' s review of such filings, including without limitation the FDA' s issuance of a " refusal to file " letter or a request for additional information; • adverse results or delays, suspensions or terminations in future preclinical studies or clinical trials; • our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial; • adverse regulatory decisions, including failure to receive regulatory approval of any of our product candidates or the failure of a regulatory authority to accept data from preclinical studies or clinical trials conducted in other countries; • changes in laws or regulations applicable to our product candidates, including but not limited to clinical trial requirements for approvals; • adverse developments concerning our manufacturers; • our inability to obtain adequate product supply for any approved product or inability to do so at acceptable prices; • our inability to establish collaborations, if needed; • our failure to commercialize our product candidates, if approved; • additions or departures of key scientific or management personnel; • unanticipated serious safety concerns related to the use of our product candidates; • introduction of new products or services offered by us or our competitors; • announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors; • our ability to effectively manage our growth; • actual or anticipated variations in quarterly operating results; • our cash position; • our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public; • publication of research reports about us or our industry, or product candidates in particular, or positive or negative recommendations or withdrawal of research coverage by securities analysts; • changes in the market valuations of similar companies; • changes in the structure of the healthcare payment systems; • overall performance of the equity markets; • sales of our common stock by us or our stockholders in the future; • trading volume of our common stock; • changes in accounting practices; • ineffectiveness of our internal controls; • disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies; • significant lawsuits, including patent or stockholder litigation; • general political and economic conditions; and • other events or factors, many of which are beyond our control. In addition, the stock market in general, and the market for biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies, including as a result of the COVID- 19 pandemic and general economic conditions. Broad market and industry factors have negatively affected and may continue to negatively affect the market price of our common stock, regardless of our actual operating performance. In the past, securities class action litigation has often been instituted against companies following periods of volatility in the market price of a company' s securities. This type of litigation, if instituted, could result in substantial costs and a diversion of management' s attention and resources. If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline. The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us or our business. We may never obtain research coverage by industry or financial analysts. If no securities or industry analysts commence coverage of our company, the trading price for our stock would likely be negatively impacted. In the event securities or industry analysts initiate coverage, if one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline. We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Furthermore, future debt or other financing arrangements may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Any return to stockholders will therefore be limited to the appreciation of their stock. **Future issuances of our common stock or the issuance of shares of common stock upon the exercise or conversion of securities that are exercisable or convertible into shares of common stock, such as our pre-funded warrants, or upon the exercise or vesting of incentive awards, may result in dilution for our stockholders. We have needed and anticipate we will need additional capital in the future to continue our planned operations. To the extent that we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities, or other equity securities in one or more transactions at prices and in a manner we determine from time to time. We also expect to issue common stock to employees, directors, and consultants pursuant to our equity incentive plans. If we sell common stock, convertible securities, or other equity securities in subsequent transactions, or common stock is issued pursuant to equity incentive plans, investors may be materially diluted. New investors in such subsequent transactions could gain rights, preferences, and privileges senior to those of holders of our common stock. As of December 31, 2023, we have outstanding pre- funded warrants to purchase 470, 000 shares of common stock at an exercise price of $ 0. 0001 per share, which may be paid by way of a cashless exercise, meaning that the holder may not pay a cash purchase price upon exercise, but instead would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the pre- funded warrant. Accordingly, we will not receive a significant amount, or potentially any, additional funds upon the exercise of the pre- funded warrants. To the extent such pre- funded warrants are exercised, additional shares of common stock will be issued for nominal or no additional consideration, which could result in substantial dilution to then existing holders of our common stock and will increase the number of shares eligible for resale in the public market. Sales of substantial**

numbers of such shares in the public market could adversely affect the market price of the common stock, causing our stock price to decline. Our issuance of additional capital stock in connection with financings, acquisitions, investments, our stock incentive plans or otherwise will dilute all other stockholders. We expect to issue additional capital stock in the future that will result in dilution to all other stockholders. We expect to grant equity awards to employees, directors and consultants under our stock incentive plans. We may also raise capital through equity financings in the future. As part of our business strategy, we may acquire or make investments in complementary companies, products or technologies and issue equity securities to pay for any such acquisition or investment. Any such issuances of additional capital stock may cause stockholders to experience significant dilution of their ownership interests and the per share value of our common stock to decline. Our executive officers, directors and their affiliates and our principal stockholders own a significant percentage of our stock and will be able to exert significant influence over matters subject to stockholder approval. Based on shares outstanding as of December 31, ~~2022~~ **2023** , our executive officers, directors and their affiliates and our principal stockholders beneficially hold, in the aggregate, approximately ~~49~~ **38** . 2 % of our outstanding voting stock. These stockholders, acting together, would be able to exert significant influence over all matters requiring stockholder approval. The concentration of voting power among these stockholders may have an adverse effect on the price of our common stock. This concentration of ownership control may adversely affect the market price of our common stock by: • delaying, deferring or preventing a change in control; • entrenching our management and the board of directors; • impeding a merger, consolidation, takeover or other business combination involving us that other stockholders may desire; and / or • discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us. Risks Related to Our Controls and Reporting Requirements We will continue to incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives. We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which require, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes- Oxley Act, as well as rules subsequently adopted by the SEC and The Nasdaq Global Select Market to implement provisions of the Sarbanes- Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial reporting controls and changes in corporate governance practices. Further, in July 2010, the Dodd- Frank Wall Street Reform and Consumer Protection Act, or the Dodd- Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd- Frank Act that require the SEC to adopt additional rules and regulations in these areas such as “ say on pay ” and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. The rules and regulations applicable to public companies substantially increase our legal and financial compliance costs and make some activities more time- consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have an adverse effect on our business. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We are a smaller reporting company, and we cannot be certain if the reduced reporting requirements applicable to smaller reporting companies will make our common stock less attractive to investors. We are a smaller reporting company as defined under SEC rules. As a smaller reporting company, we are able to take advantage of certain exemptions from disclosure requirements, including reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and providing only two years of audited financial statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock. We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management’ s assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to restatements of our financial statements and require us to incur the expense of remediation. Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision- making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected. We have broad discretion over the use of our cash and cash equivalents and may not use them effectively. Our management has broad discretion to use our cash and cash equivalents to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending our use to fund operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value. Risks Related to Charter and Bylaws Anti- takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management. Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include: • a board of directors divided into three classes serving staggered three- year terms, such that not all members of the board will be elected at one time; • a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders; • a requirement that special meetings of stockholders be called only by the board of directors acting pursuant to a resolution approved by the affirmative vote of a majority of the directors then in office; • advance notice requirements for stockholder proposals and nominations for election to our board of directors; • a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two- thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors; • a requirement of approval of not less than two- thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action or to amend specific provisions of our certificate of incorporation; and • the authority of the board of directors to issue convertible preferred stock on terms determined by the board of directors without stockholder approval and which convertible preferred stock may include rights superior to the rights of the holders of common stock. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which may prohibit certain business combinations with stockholders owning 15 % or more of our outstanding voting stock. These anti- takeover provisions and other provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then- current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors of your choosing or cause us to take other corporate actions you desire. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline. Our amended and restated bylaws designate certain courts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees. Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of fiduciary duty owed by any of our directors, officers and employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the DGCL, our amended and restated certificate of incorporation or our bylaws (in each case, as they may be amended from time to time) or (iv) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein; provided, however, that this exclusive forum provision will not apply to any causes of action arising under the Securities Act or the Exchange Act, or any other claim for which the federal courts have exclusive jurisdiction; and provided further that, if and only if the Court of Chancery of the State of Delaware dismisses any such action for lack of subject matter jurisdiction, such action may be brought in another state or federal court sitting in the State of Delaware, or any other claim for which the federal courts have exclusive jurisdiction; and provided further that, if and only if the Court of Chancery of the State of Delaware dismisses any such action for lack of subject matter jurisdiction, such action may be brought in another state or federal court sitting in the State of Delaware. Our amended and restated bylaws also specify that unless we consent in writing to the selection of an alternate forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the foregoing provisions. We recognize that the forum selection clause in our bylaws may impose additional litigation costs on stockholders in pursuing any such claims. Additionally, the forum selection clause in our bylaws may limit our stockholders’ ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. The enforceability of similar choice of forum provisions in other companies’ governing documents has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our bylaws to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition, or results of operations.