Risk Factors Comparison 2025-03-20 to 2024-03-28 Form: 10-K

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

You should carefully consider the following risk factors, together with all other information in this report, including our consolidated financial statements and notes thereto, and in our other filings with the SEC. If any of the following risks, or other risks not presently known to us or that we currently believe to not be material, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common stock could decline, and stockholders may lose all or part of their investment. Risks Related to Our Business We have no approved products and depend on the future success of the product candidates in our research and development pipeline. We cannot be certain that we or our collaborators will be able to obtain regulatory approval for, or successfully commercialize, product candidates from our current pipeline or any other product candidates that we may subsequently identify, license or otherwise acquire. We and our collaborators are not permitted to market or promote any products in the United States, Europe, China or other countries before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for our current product candidates. We have not submitted a new drug application (NDA) to the FDA or comparable applications to other regulatory authorities and do not expect to be in a position to do so in the near future. All ~~of~~ our product candidates are in clinical development or in varying stages of nonclinical development. Data supporting our ~~drug discovery and nonclinical and~~ clinical development programs are derived from ~~laboratory studies,~~ nonclinical ~~studies and Phase 1~~ **data that support our early stage** clinical **programs** ~~studies. It may be years before the larger~~ , **which will determine whether** pivotal studies **are appropriate. These pivotal studies are** necessary to support regulatory approval ~~of our current product candidates~~ **, and it may be years before these larger, pivotal studies** are completed, if ever. In addition to our current product pipeline, we may identify, license or otherwise acquire rights to other technologies or product candidates. Any such transactions would involve numerous risks, and we may be unsuccessful in entering into any such transactions or developing any such technologies or product candidates. For these reasons, our drug discovery and development may not be successful, and we may be unable to continue clinical development of our product candidates and may not generate product approvals or product revenue, any of which could have a material adverse impact on our business, results of operations and financial condition. We are not currently profitable and might never become profitable, and we will need additional financing to complete the development of any product candidates and fund our activities into the future. We do not have any approved products, and we have a history of losses. We expect to continue to incur substantial operating and capital expenditures to advance our current product candidates through clinical development, continue research and discovery efforts to identify potential additional product candidates and seek regulatory approvals for our current and future product candidates. All operations and capital expenditures will be funded from cash on hand, securities offerings, debt financings and payments we may receive from out- licenses, collaborations or other strategic arrangements. ~~Elevated worldwide~~ **Adverse geopolitical and macroeconomic developments, such as ongoing military conflicts, related sanctions, actual and anticipated changes in interest rates, economic** inflation ~~rates that began in mid- 2021~~ and ~~continue to persist may also exacerbate~~ the ~~substantial operating and~~ **responses by central banking authorities to control such inflation, could affect our ability to access** capital **as** ~~expenditures that we face to advance our current~~ and **when needed** ~~future product candidates~~ . There is no assurance that we will be successful in raising any necessary additional capital on terms that are acceptable to us, or at all ~~, particularly due to the well- documented, ongoing sector- wide weakness in the biotech markets that began in early 2021~~ . If we are unable to develop and commercialize any product candidates and generate sufficient revenue or raise capital, we could be forced to reduce staff, delay, scale back or discontinue product development and clinical studies, sacrifice attractive business opportunities, cease operations entirely and sell, or otherwise transfer, all or substantially all of our remaining assets, which would likely have a material adverse impact on our business, results of operations, financial condition and share price. We expect our collaboration with Gilead to be a critical part of the development, manufacture and commercialization of our product candidates. If this collaboration is unsuccessful, our business could be adversely affected. In October 2023, we entered into the Gilead Collaboration Agreement with Gilead, whereby Gilead exclusively licensed to us its HPI program and NNPI program, while retaining opt- in rights to these programs, and **has** ~~will have~~ an option to take an exclusive license, on a program- by- program basis, to all of our other current and future pipeline programs during the collaboration term. In connection with the entry into the Gilead Collaboration Agreement, we and Gilead also entered into a common stock purchase agreement and an investor rights agreement **, which were both amended in June 2024. Also in June 2024, we and Gilead subsequently entered into a securities purchase agreement and warrant agreement. In December 2024, Gilead purchased additional shares of our common stock at a premium pursuant to the terms of the common stock purchase agreement, and we amended the Gilead Collaboration Agreement in connection with an updated development plan for 6250** . Our agreements and relationship with Gilead pose a number of risks, including, but not limited to, the following: • Conflicts may arise between us and Gilead, such as conflicts regarding the indications to pursue or concerning the clinical data supporting an opt- in decision, the commercial potential of any optioned investigational products, the interpretation of financial provisions or the ownership of intellectual property developed during the collaboration. Any such conflicts could slow or prevent the development or commercialization of our investigational products. • If the collaboration with Gilead does not result in the successful development and commercialization of products or if Gilead terminates the Gilead Collaboration Agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, ~~our~~ development of our investigational products could be delayed and we may need

additional resources to develop our investigational products. • We will be heavily dependent on Gilead for further development and commercialization of the investigational products from the programs that it opts into. • We may not be successful in this collaboration due to various other factors, including our ability to demonstrate proof of concept in one or more clinical studies so that Gilead will exercise its option to these programs. In addition, even if we demonstrate clinical proof of concept of a candidate, Gilead may choose not to exercise its option. • Gilead has the right to designate **(and has designated)** two directors for appointment to our board of directors pursuant to the terms of the investor rights agreement and owns approximately ~~19~~ **29** . 9 % of our outstanding common stock. Gilead also has the right to acquire additional shares ~~from us, and~~ in the open market, up to an amount resulting in Gilead owning a total of 35 % of our outstanding common stock. As a result, Gilead may be able to exert significant influence over us. • Gilead could independently develop, or develop with third parties, products that compete directly or indirectly with our investigational products if Gilead believes that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours. • Because Gilead has an option to all ~~of~~ our current, and future, pipeline programs during the collaboration term, it may be difficult for us to enter into new collaborations. Nonclinical and clinical studies required for our product candidates are expensive and time- consuming and may fail to demonstrate the level of safety and efficacy necessary for product approval. Before we or any commercial partners can obtain FDA approval (or other foreign approvals) necessary to sell any of our product candidates, we must show that each potential product is safe and effective. To meet these requirements, we must conduct extensive nonclinical and sufficient, well- controlled clinical studies. The results of ~~laboratory and~~ nonclinical studies may not be representative of disease behavior in a clinical setting and may not be predictive of the outcomes of our clinical studies. In addition, the results of early clinical studies of product candidates may not be predictive of the results of later- stage clinical studies. Conducting nonclinical and clinical studies is a lengthy, time consuming and expensive process. The length of time varies substantially according to the type, complexity, novelty, and intended use of the product candidate, and often can be several years or more. In addition, failure or delays can occur at any time during the nonclinical and clinical study process, resulting in additional operating expenses or harm to our business. The commencement and rate of completion of clinical studies might be delayed by many factors, including, for example: • delays in reaching agreement with regulatory authorities on study design; • delays in reaching agreement on acceptable terms with prospective **contract research organizations (** CROs **)** and clinical study sites; • failure to demonstrate efficacy or the emergence of unforeseen safety issues; • insufficient quantities of qualified materials ~~under~~ **made using** current good manufacturing practice (cGMP) for use in clinical studies due to manufacturing challenges, delays or interruptions in the supply chain; • slower than expected rates of ~~patient~~ **participant** recruitment or failure to recruit a sufficient number of eligible ~~patients~~ **participants** , which may be due to a number of reasons, including the size of the ~~patient~~ **participant** population, the proximity of ~~patients~~ **participants** to clinical sites, the eligibility criteria for the study, the design of the clinical study, and other potential drug candidates being studied; • **fewer available study sites due to changes in government funding of clinical research; •** delays in ~~patients~~ **participants** completing participation in a study or return for post- treatment follow- up for any reason, including, product side effects or disease progression; • modification of clinical study protocols; • delays, suspension, or termination of clinical studies by the institutional review board or ethics committee responsible for overseeing the study at a particular study site; and • government or other regulatory agency delays or clinical holds requiring suspension or termination of our clinical studies due to safety, tolerability or other issues related to our product candidates. The failure of nonclinical and clinical studies to demonstrate safety and effectiveness of a product candidate for the desired indications, whether conducted by us or by a CRO, would harm the development of that product candidate and potentially other product candidates. This failure could cause us to abandon a product candidate and could delay development of other product candidates. Any delay in, or failure of, our nonclinical studies or clinical studies could delay, or preclude, the filing of our NDAs and comparable applications with the FDA and foreign regulatory agencies, as applicable, and materially harm our business, prospects, financial condition and results of operations. We rely on CROs to conduct some of our nonclinical and clinical studies due to our lack of suitable facilities and resources. In addition, parts of our business are reliant on CROs, vendors, suppliers and other service providers in locations outside of the United States, including China. We do not have sufficient facilities or resources to conduct all our anticipated nonclinical and clinical studies internally. As a result, we contract with CROs to conduct a significant portion of the nonclinical and clinical studies required for regulatory approval for our product candidates. Our reliance on CROs reduces our control over these activities but does not relieve us of our responsibilities. For example, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, including, in the case of clinical studies, good clinical practices, even if the study is conducted by a CRO. In the event CROs fail to perform their duties in such a fashion or we are unable to retain or continue with CROs on acceptable terms, we may be unable to complete our clinical studies and may fail to obtain regulatory approval for our product candidates. In addition, these CROs may also have relationships with other entities, some of which may be our competitors. CRO personnel are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether they devote sufficient time and resources to our clinical and nonclinical studies. If these CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements **, including good clinical practices,** or for other reasons, our research, nonclinical or clinical studies may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates, any of which could materially harm our business, prospects, financial condition and results of operations. Furthermore, we are exposed to a number of risks related to our CROs, vendors, suppliers and other service providers that are located outside of the United States, many of which may be beyond our control. These risks include: • business interruptions resulting from geopolitical actions such as the war between Russia and Ukraine, the ~~Israel- Hamas war~~ **conflicts in the Middle East, the rising tensions between China and Taiwan** , as well as tariffs, other wars, acts of terrorism,

natural disasters or outbreaks of disease; • different regulatory requirements for drug approvals or increased scrutiny on CROs located in foreign countries, including China; • different standards of care in various countries that could complicate the evaluation of our product candidates; • different U. S. and foreign drug import and export rules; • different reimbursement systems and different competitive drugs indicated to treat the indication for which our product candidates are being developed; • reduced protection for intellectual property rights in certain countries; • **Changes in economic policies by the U. S. or foreign governments, which may result in new or** unexpected changes in tariffs, trade barriers ~~and~~ **or** regulatory requirements; • compliance with the United States Foreign Corrupt Practices Act (the FCPA) and other anti- corruption and anti- bribery laws; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign taxes, including withholding of payroll taxes; and • foreign currency fluctuations and compliance with foreign currency exchange rules, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country. Top- line ~~or ,~~ preliminary **or interim** data may not accurately reflect the final results of a particular study. We may publicly disclose top- line ~~or ,~~ preliminary **or interim** data based on analysis of then- available efficacy, tolerability, PK and safety data, and the results and related findings and conclusions are subject to change following a more comprehensive **data** review ~~of the data~~ related to the particular study. We also **may** make assumptions, estimates, calculations and conclusions as part of our data analyses, and we may not have received or had the opportunity to fully and carefully evaluate all data prior to release. As a result, the top- line ~~or ,~~ preliminary **or interim** results that we report may differ from final results of the same studies or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. Top- line **, preliminary or interim** data also ~~remains~~ **remain** subject to audit and verification procedures that may result in the final data differing materially from previously published **top- line,** preliminary **or interim** data. As a result, top- line ~~and ,~~ preliminary **or interim** data should be viewed with caution until the final data are available. In addition to top- line ~~or~~ **,** preliminary **or interim** results, the information that we may publicly disclose regarding a particular nonclinical or clinical study is based on extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure. In addition, 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 drug, drug candidate or our business. If the top- line ~~or ,~~ preliminary **or interim** data that we report differ from final results, or if others, including regulatory authorities, disagree with, or do not accept, the data or conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed or delayed, which could harm our business, financial condition, operating results or prospects. We rely on third parties to formulate and manufacture our product candidates and products that we study in combination with our product candidates. Our use of third parties may increase the risk that we will not have sufficient quantities of our product candidates or other products on time or at an acceptable cost. We rely on third- party manufacturers to supply the quantities of our investigational product candidates used in our clinical and nonclinical studies. If any product candidate we develop or acquire in the future receives FDA or other regulatory approval, we expect to continue our reliance on one or more third- party contractors to manufacture our products. If, for any reason, we are unable to rely on any third- party sources we have identified to manufacture our product candidates, we would need to identify and contract with additional or replacement third- party manufacturers to manufacture drug substance and drug product for nonclinical, clinical and commercial purposes. We may be unsuccessful in identifying additional or replacement third- party manufacturers, or in negotiating acceptable terms with any that we do identify. If we are unable to establish and maintain manufacturing capacity, the development and sales of our products and our financial performance may be materially and adversely affected. We are exposed to the following risks with respect to the manufacture of our product candidates: • We will need to identify manufacturers for commercial supply on acceptable terms, which we may be unable to do because the number of potential manufacturers is limited, and the FDA must evaluate and approve any new or replacement contractor. • Any third- party manufacturers with whom we contract might be unable to formulate and manufacture our product candidates in the volume and quality required to meet our nonclinical, clinical and, if approved, commercial needs in a timely manner. • Any third- party manufacturers with whom we contract might not perform as agreed or might not remain in the contract manufacturing business for the time required to supply our products. • One or more of any third- party manufacturers with whom we contract could be foreign, which increases the risk of shipping delays and adds the risk of import restrictions. • We do not have complete control over, and cannot ensure, any third- party manufacturers' compliance with cGMP and other government regulations and corresponding foreign requirements, including periodic FDA and state regulatory inspections. • We may be required to obtain intellectual property rights from third parties to manufacture our product candidates, and if any third- party manufacturer makes improvements in the manufacturing process for our product candidates, we may not own, or may have to share, the intellectual property rights to the innovation. • We may be required to share our trade secrets and know- how with third parties, increasing risk of misappropriation or disclosure of our intellectual property by or to third parties. • When contracting with third- party manufacturers, we might compete with other companies for access to these manufacturers' facilities and might be subject to manufacturing delays if the manufacturers give other clients higher priority than we are given. Each of these risks could delay our development efforts, nonclinical studies and clinical studies or the approval, if any, of our product candidates by the FDA or applicable non- U. S. regulatory authorities and the commercialization of our product candidates **. Furthermore, reductions in workforce at the FDA may lead to delays in inspecting facilities and, in turn, delayed FDA approvals for manufacturing changes** . This could result in higher costs or deprive us of potential product revenues and materially harm our business, financial condition and results of operations. If we lose key management personnel and cannot recruit and retain similarly qualified replacements, our business may materially suffer. We are highly dependent on the services of our executive officers. Our employment agreements with our executive officers do not ensure their retention. We do not currently maintain, nor do we intend to obtain in the future, " key person " life insurance that would compensate us in the event of the death or disability of any of the members of our management team. Our executive officers are critical to our success, and unanticipated loss of any of

these key employees could have a material adverse impact on our business, financial condition and results of operations. Our collaboration partners might delay, prevent or undermine the success of our product candidates. Our operating and financial strategy for the development, nonclinical and clinical testing, manufacture and commercialization of drug candidates heavily depends on collaborating with corporations, academic institutions, licensors, licensees, and other parties. However, there can be no assurance that we will successfully establish or maintain these collaborations. If a collaboration is terminated, replacement collaborators might not be available on attractive terms, or at all. The activities of any collaborator, including Gilead, will not be within our control and might not be within our power to influence. There can be no assurance that any collaborator will perform its obligations to our satisfaction or at all, that we will derive any revenue or profits from these collaborations, or that any collaborator will not compete with us. If any collaboration, including the Gilead Collaboration, is unsuccessful, we might require substantially greater capital to undertake development and marketing of our proposed products and might not be able to develop and market these products effectively, if at all. In addition, if Gilead does not opt- in to a program, it might lead to significant delays in introducing proposed products into certain markets and / or reduced sales of proposed products in such markets. We may not be successful in establishing and maintaining collaborations, which could adversely affect our ability to develop certain of our product candidates. Developing pharmaceutical products, conducting clinical studies, obtaining regulatory approval and commercializing those products are expensive and lengthy undertakings that require significant resources and expertise. We may seek to enter into collaborations, including licensing or partnering arrangements, with other companies to support the development and commercialization of any or multiple of our programs that Gilead declines to opt into or to obtain financing or share costs on these programs. If we are unable to enter into such collaborations on acceptable terms, if at all, we may be unable to advance certain of our product candidates through further nonclinical or clinical development. We expect to face competition in seeking appropriate partners. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement and they may require substantial resources to maintain. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements for the development of our product candidates that Gilead declines to opt into. If we are unable to reach agreement on favorable terms with a suitable collaboration partner for any of our product candidates that Gilead declines to opt into, we may need to limit the number of our product candidates to advance through further nonclinical or clinical development. Failure to achieve such successful collaborations would limit our options for support of the development and commercialization of our programs and for financing and would likely have a material adverse impact on our business, results of operations, financial condition and share price. We rely on data provided by third parties that has not been independently verified and could prove to be false, misleading, or incomplete. We rely on third- party vendors, scientists, investigators and collaborators to provide us with significant data and other information related to our projects, nonclinical studies and clinical studies, and our business. If these third parties provide inaccurate, misleading, or incomplete data, our business, prospects, and results of operations could be materially and adversely affected. Significant disruptions of information technology systems or breaches of data security, including cybersecurity incidents, could materially and adversely affect our business, results of operations and financial condition. We collect and maintain information in digital form and are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We have outsourced elements of our information technology infrastructure and, as a result, a number of third- party vendors may or could have access to our confidential information. Our internal information technology systems and infrastructure, and those of our current and any future collaborators, contractors and consultants and other third parties on which we rely, are vulnerable to damage from computer viruses, malware, natural disasters, **system outages,** terrorism, war, telecommunication and electrical failures, cyberattacks, cybersecurity incidents or cyber intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a cybersecurity incident or security breach or disruption, particularly through cyberattacks or cyber intrusion, has escalated as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information or other intellectual property. The costs to us to mitigate network security problems, bugs, viruses, worms, malicious software programs **, system outages** and security vulnerabilities or incidents could be significant, and our efforts to address these problems may not be successful. If unsuccessful, these problems could cause interruptions, delays, cessation of service and other harm to our business and our competitive position, including material disruption of our product development programs. For example, any loss of clinical study data from completed or ongoing or planned clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. If a computer security breach affects our systems or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal, state and non- U. S. privacy and security laws, if applicable, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Clinical Health Act of 2009, and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission, state breach notification law and the **European Union (EU) General Data Protection Regulation (** EU GDPR **)** . We would also be exposed to a risk of loss or litigation and potential liability, which could materially adversely affect our business, results of operations and financial condition. Research, development and commercialization goals **, including data releases,** may not be achieved in the timeframes that we publicly estimate, which could have an adverse impact on our business and could cause our stock price to decline. We set goals and make public statements regarding our expectations on timing of certain accomplishments, developments and milestones under our research and development programs. The actual timing of these

events can vary significantly due to a number of factors, including, the amount of time, effort and resources committed to our programs by us and any collaborators and the uncertainties inherent in the clinical development and regulatory approval process. As a result, there can be no assurance that we or any collaborators will initiate or complete clinical development activities, make regulatory submissions or receive regulatory approvals as planned or that we or any collaborators will be able to adhere to our current schedule for the achievement of key milestones under any of our programs. If we or any collaborators fail to achieve one or more of the milestones as planned, or Gilead does not opt- in to any of our programs, our business could be materially and adversely affected, and the price of our common stock could decline. Developments by competitors might render our product candidates or technologies obsolete or non- competitive. The pharmaceutical and biotechnology industries are intensely competitive. In addition, the clinical and commercial landscapes for recurrent genital herpes, HDV, HBV and transplant- related herpesviruses are rapidly changing; we expect new data from commercial and clinical- stage products to continue to emerge. We compete with organizations, some with significantly more resources, who are developing competitive product candidates. If our competitors develop effective treatments for recurrent genital herpes, HDV, HBV ~~,~~ **and** transplant- related herpesviruses or any other indication or field we might pursue, and successfully commercialize those treatments, our business and prospects could be materially harmed. Other companies with products using the same or similar mechanisms of action as ours may produce negative clinical data, which would adversely affect public and clinical communities' perceptions of our product candidates, and may negatively impact regulatory approval of, or demand for, our potential products. Negative data from clinical studies using a competitor' s product candidates with the same or similar mechanisms of action **(MOA)** as ours could adversely impact the perception of the therapeutic use of our product candidates and our ability to enroll ~~patients~~ **individuals** in clinical studies. The clinical and commercial success of our potential products will depend in part on the public and clinical communities' acceptance of novel classes of product candidates. Moreover, our success depends upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of our product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which more clinical data may be available. Adverse events in our nonclinical or clinical studies or those of our competitors or of academic researchers utilizing the same **MOA** ~~mechanisms of action~~ as our product candidates, even if not ultimately attributable to our product candidates, and any resulting publicity could result in increased governmental regulation **, larger, more complex, or an increased number of clinical trial requirements** , unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for our product candidates that are approved, if any, and a decrease in demand for any such products. Our ability to use our net operating loss and credit carryforwards and certain other tax attributes may be limited. We have net operating loss carryforwards due to prior period losses generated before January 1, 2024 **,** which if not utilized **,** will begin to expire in ~~2027~~ **2029** for net operating loss carryforwards prior to 2018. If we are unable to generate sufficient taxable income to utilize our net operating loss carryforwards, pre- 2018 carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), a corporation that undergoes an " ownership change " (generally defined as a greater than 50 % change (by value) in its equity ownership over a three- year period) is subject to annual limitations on its ability to use its pre- change net operating loss carryforwards and other pre- change tax attributes (such as research tax credits) to offset its post- change income or taxes. We have experienced ownership changes in the past, and ~~recent and~~ future equity issuances may result in additional ownership change. Accordingly, some of our net operating losses or credits could expire unutilized, and our ability to utilize our net operating losses or credits to offset U. S. federal taxable income could be limited, which would result in increased future tax liability to us. We may also be subject to similar limitations at the state level. Risks Related to Our Regulatory and Legal Environment We are and will be subject to extensive and costly government regulation **,** and the failure to comply with these regulations may have a material adverse effect on our operations and business. Our product candidates are subject to extensive and rigorous domestic government regulation, including regulation by the FDA, the Centers for Medicare and Medicaid Services, other divisions of the U. S. Department of Health and Human Services, the U. S. Department of Justice, state and local governments, and their respective foreign equivalents. Both before and after approval of any product, we and our collaborators, suppliers, contract manufacturers and clinical investigators are subject to extensive regulation by governmental authorities in the United States and other countries, covering, among other things, testing, manufacturing, quality control, clinical studies, post- marketing studies, labeling, advertising, promotion, distribution, import and export, governmental pricing, price reporting and rebate requirements. Failure to comply with applicable requirements could result in one or more of the following actions: warning or untitled letters; unanticipated expenditures; delays in approval or refusal to approve a product candidate; voluntary or mandatory product recall; product seizure; interruption of manufacturing or clinical studies; operating or marketing restrictions; injunctions; criminal prosecution and civil or criminal penalties, including fines and other monetary penalties; exclusion from federal health care programs such as Medicare and Medicaid; adverse publicity; and disruptions to our business. If we or our collaborators obtain regulatory approval for a particular product, the approval might limit the intended medical uses for the product, limit our ability to promote, sell, and distribute the product, require that we conduct costly post- marketing surveillance, and / or require that we conduct ongoing post- marketing studies. Once obtained, any approvals might be withdrawn, including, for example, if there is a later discovery of previously unknown problems with the product, such as a previously unknown safety issue. If we, our collaborators, our contractors or our contract manufacturers fail to comply with applicable regulatory requirements at any stage during the regulatory process, such noncompliance could result in delays in the approval of applications or supplements to approved applications, refusal by a regulatory authority (including the FDA) to review pending ~~market~~ **marketing** ~~approval~~ **authorization** applications or supplements to approved applications, untitled letters or warning letters, fines, import and export restrictions, product recalls or seizures, injunctions, total or partial suspension of production, civil penalties, withdrawals of previously approved marketing ~~applications~~ **authorizations** , recommendations by the FDA or other regulatory authorities against governmental contracts, and / or criminal prosecutions. The regulatory approval processes of the FDA and comparable

foreign authorities are lengthy, time consuming and inherently unpredictable, and if we or our collaborators are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed. We, or any current or future collaborators, cannot assure you that we will receive the approvals necessary to commercialize for sale any of our product candidates, or any product candidate we acquire or develop in the future. We will need FDA approval to commercialize our product candidates in the United States and approvals from applicable regulatory authorities in foreign jurisdictions to commercialize our product candidates in those jurisdictions. To obtain FDA approval of any product candidate, we must submit to the FDA an NDA demonstrating that the product candidate is safe and effective for its intended use. This requires significant research, nonclinical studies, and clinical studies. Satisfaction of the FDA' s regulatory requirements typically takes many years, depends upon the type, complexity and novelty of the product candidate and requires substantial resources for research, development and testing. We cannot predict whether our research and clinical approaches will result in drugs that the FDA considers safe and effective for their indicated uses. The FDA has substantial discretion in the approval process and might require us to conduct additional nonclinical and clinical testing, perform post- marketing studies or otherwise limit or impose conditions on any approval we obtain. The **ability of the FDA to review and** ~~approval~~ **approve new products can be affected by a variety of factors, including government budget and funding levels, authorization and payment of user fees, the ability to hire and retain key personnel, as well as other statutory, regulatory and policy changes. In addition, funding of other government agencies that support research and development activities that pertain to FDA review, such as research to understand new technologies or establish new standards, can shift in response to changing administrative policies and priorities. Such policy shifts, including efforts to downsize the federal workforce, remove job elimination protections for federal workers, limit certain communications, and potentially interfere with user fee reauthorization, may affect the FDA review** process ~~might also be delayed by changes in~~ **and average review times at the FDA may fluctuate as a result. If a prolonged** government **shutdown or a widespread freeze on federal funding occurs, it could significantly impact the ability of the FDA to timely review and process our** ~~regulation~~ **regulatory submissions , the National Institutes of Health to conduct research or provide grants, or other agencies that support the FDA to slow their work. In addition, if** future legislation or administrative action or changes in FDA policy **prevent the FDA** ~~that occur prior to or during our~~ **or other** regulatory **authorities from conducting routine inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA to timely** review **and process our regulatory submissions, which could have a material adverse effect on our business** . Delays in obtaining regulatory approvals might: delay commercialization of, and our ability to derive product revenues from, our product candidates; impose costly procedures on us; and diminish any competitive advantages that we might otherwise enjoy. Even if we comply with all FDA requests, the FDA might ultimately reject one or more of our NDAs. We cannot be sure that we will ever obtain regulatory approval and commercialize any of our current or future product candidates. In foreign jurisdictions, we are subject to regulatory approval processes and risks similar to those associated with the FDA described above. We cannot assure you that we will receive the approvals necessary to commercialize our product candidates for sale outside the United States. We and our collaborators may be subject, directly or indirectly, to applicable U. S. federal and state anti- kickback, false claims laws, physician payment transparency laws, fraud and abuse laws or similar healthcare and security laws and regulations, and health information privacy and security laws, which could expose us or them to criminal sanctions, civil penalties **, exclusion or suspension from federal and state healthcare programs** , contractual damages, reputational harm and diminished profits and future earnings. Healthcare providers, physicians and others play a primary role in the recommendation and prescription of any products for which we obtain regulatory approval. If we obtain FDA approval for any of our drug candidates and begin commercializing those drugs in the United States, our operations may be subject to various federal and state fraud and abuse laws, including the federal Anti- Kickback Statute, the federal False Claims Act, and physician payment sunshine laws and regulations. Additionally, we are subject to state and non- U. S. equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states and foreign jurisdictions in which we conduct our business. If we fail to comply with any applicable federal, state or foreign legal requirement, we could be subject to penalties. Regulators globally are imposing greater monetary fines for privacy violations. The EU GDPR applies to any company established in the EU as well as to those outside the EU if they collect and use personal data in connection with the offering **of** goods or services to individuals in the EU or the monitoring of their behavior. The EU GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on services providers. Noncompliance with the EU GDPR may result in monetary penalties of up to € 20 million or 4 % of worldwide revenue, whichever is higher. The EU GDPR may increase our responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms to ensure compliance with the EU GDPR, including as implemented by individual countries. Compliance with the EU GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase our cost of developing our products or even prevent us from offering certain products in jurisdictions that we may operate in. The California Consumer Privacy Act (CCPA) also created new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA requires covered companies to provide certain disclosures to consumers about its data collection, use and sharing practices, and to provide affected California residents with ways to opt- out of certain sales or transfers of personal information. While there is currently an exception for protected health information that is subject to HIPAA and clinical study regulations, as currently written, the CCPA may impact our business activities. The uncertainty surrounding the implementation of the CCPA exemplifies the vulnerability of our business

to the evolving regulatory environment related to personal data and protected health information. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Violations of these laws may be punishable by criminal and / or civil sanctions, including penalties, fines and / or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U. S. government. In addition, private individuals have the ability to bring actions on behalf of the U. S. government under the federal False Claims Act as well as under the false claims laws of several states. If any of the physicians or other providers or entities with whom we expect to do business with are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business. We face the risk of product liability claims and might not be able to obtain insurance. Our business exposes us to the risk of product liability claims that are inherent in drug development. If the use of one or more of our product candidates or approved drugs, if any, harms people, we might be subject to costly and damaging product liability claims brought against us by clinical study participants, consumers, health care providers, pharmaceutical companies or others selling our products. Our inability to obtain sufficient product liability / clinical study insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of pharmaceutical products we develop. We cannot predict all of the possible harms or side effects that might result and, therefore, the amount of insurance coverage we maintain might not be adequate to cover all liabilities we might incur. If we are unable to obtain insurance at an acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which might materially and adversely affect our business and financial position. If we are sued for any injury allegedly caused by our products, our liability could exceed our total assets and our ability to pay. Any successful product liability claims brought against us would decrease our cash and may adversely affect our business, stock price and financial condition. We might be exposed to liability claims associated with the use of hazardous materials and chemicals. Our research, development and manufacturing activities and / or those of our third- party contractors might involve the controlled use of hazardous materials and chemicals. Although we will strive to have our safety procedures, and those of our contractors, comply with federal, state and local laws and regulations for using, storing, handling and disposing of these materials, we cannot completely eliminate the risk of accidental injury or contamination from these materials. In the event of such an accident, we could be held liable for any resulting damages, and any liability could materially and adversely affect our business, financial condition and results of operations. In addition, the federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous or radioactive materials and waste products might require us to incur substantial compliance costs that could materially and adversely affect our business, financial condition and results of operations. Our employees, independent contractors, consultants, collaborators and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could result in significant liability for us and harm our reputation. We are exposed to the risk of fraud or other misconduct, including failure to: • comply with applicable regulations of, and provide accurate information to, the FDA or comparable foreign regulatory authorities; • comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities; • comply with the FCPA, the U. K. Bribery Act 2010, the PRC Criminal Law, the PRC Anti- unfair Competition Law and other anti- bribery and trade laws; • report financial information and data accurately; or • disclose unauthorized activities. Misconduct could also involve the improper use or misrepresentation of information obtained during clinical studies, creating fraudulent data in our nonclinical studies or clinical studies or illegal misappropriation of product materials, which could result in regulatory sanctions, delays in clinical studies, or serious harm to our reputation. It is not always possible to identify and deter misconduct. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with such laws 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 harm our business, results of operations, financial condition and cash flows, including through the imposition of significant fines or other sanctions. Risks Related to Our Intellectual Property Our business depends on protecting our intellectual property. If we, our licensors and our collaborators do not obtain protection for our respective intellectual property rights, our competitors might be able to take advantage of our research and development efforts to develop competing drugs. Our success, competitive position and future revenues, if any, depend in part on our ability and the abilities of our licensors to obtain and maintain patent protection for our products, methods, processes and other technologies, to preserve our trade secrets, to prevent third parties from infringing on our proprietary rights and to operate without infringing the proprietary rights of third parties. We rely upon a combination of patents, trade secret protection and contractual arrangements to protect the intellectual property related to our technologies. We will only be able to protect our products and proprietary information and technology by preventing unauthorized use by third parties to the extent that our patents, trade secrets, and contractual positions allow us to do so. We cannot be certain that we will secure any rights to any issued patents with claims that cover any of our proprietary product candidates and technologies. The patent prosecution process is expensive and time- consuming, and we may be unable to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We could fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection or before our competitors secure patents covering such discoveries. The patent process also is subject to numerous risks and uncertainties, and there can be no assurance that we will be successful in protecting our products by obtaining and defending patents. Composition- of- matter patents relating to the active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products. Such patents provide protection not limited to any one method of use. Method- of- use patents protect the use of a product for the specified method (s) and do not prevent a

competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Formulation patents protect the formulation of a product and do not prevent a competitor from making and marketing a product that has an identical active pharmaceutical ingredient to our product if the product is formulated differently than the patented formulation. We rely on a combination of these and other types of patents to protect our product candidates, and there can be no assurance that our intellectual property will create and sustain the competitive position of our product candidates. Biotechnology and pharmaceutical product patents involve highly complex legal and scientific questions. Any patent applications that we own or license may fail to result in issued patents. In addition, the U. S. Patent and Trademark Office (USPTO) and patent offices in other jurisdictions often require that patent applications concerning pharmaceutical and / or biotechnology- related inventions are limited or narrowed substantially to cover only the specific innovations exemplified in the patent application, thereby limiting the scope of protection against competitive challenges. As a result, even if we or our licensors obtain patents, the patents might be substantially narrower than anticipated. If patents successfully issue from our applications, third parties may challenge their validity or enforceability, which may result in such patents being narrowed, invalidated, or held unenforceable. Even if our patents and patent applications are not challenged by third parties, those patents and patent applications may not prevent others from designing around our claims and may not otherwise adequately protect our product candidates. Patent and other intellectual property protection is crucial to the success of our business and prospects, and there is a substantial risk that such protections, if obtained, will prove inadequate. The legal systems of certain countries, including China, do not always favor the enforcement of patents, trade secrets, and other intellectual property rights, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop infringement of our patents, misappropriation of our trade secrets, or marketing of competing products in violation of our proprietary rights. Beyond the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know- how, information, or technology that is not covered by our patents. Although our agreements require all of our employees to assign their inventions to us, and we require all of our employees, consultants, advisors, collaborators, contractors and any third parties who have access to our trade secrets, proprietary know- how and other confidential information and technology to enter into appropriate confidentiality agreements, we cannot be certain that our trade secrets, proprietary know- how and other confidential information and technology will not be subject to unauthorized disclosure or that our competitors will not otherwise gain access to or independently develop substantially equivalent trade secrets, proprietary know-how and other information and technology. If we are unable to prevent unauthorized disclosure of our intellectual property related to our product candidates and technology to third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business and operations. We may incur substantial costs as a result of litigation or other proceedings relating to our patents and other intellectual property rights. We may in the future be involved in legal or administrative proceedings involving our intellectual property, including infringement of our intellectual property by third parties. These lawsuits or proceedings likely would be expensive, consume time and resources and divert the attention of managerial and scientific personnel, even if we were successful in stopping the infringement of such patents. There is a risk that these proceedings will decide that such patents or other intellectual property rights are not valid and that we do not have the right to stop the other party from using our inventions. There is also the risk that, even if the validity of such patents is upheld, the court or administrative agency will refuse to stop the other party on the ground that such other party' s activities do not infringe our rights to such patents. If we were not successful in defending our intellectual property, our competitors could develop and market products based on our discoveries, which may reduce demand for our products. We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our product candidates. Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. Our competitors may have filed, and may in the future file, patent applications covering products and technologies similar to ours. Any such patent application may have priority over our patent applications, which could further require us to obtain rights from third parties to issued patents covering such products and technologies. We cannot guarantee that the manufacture, use or marketing of any product candidates that we develop will not infringe third- party patents. If a patent infringement suit were brought against us, we may be forced to stop or delay developing, manufacturing, or selling potential products that are claimed to infringe a third party' s intellectual property, unless that third party grants us rights to use its intellectual property. In such cases, we may be required to obtain licenses to patents or proprietary rights of others to continue development, manufacture or sale of our products. If we are unable to obtain a license or develop or obtain non- infringing technology, or if we fail to defend an infringement action successfully, or if we are found to have infringed a valid patent, we may incur substantial costs and monetary damages, encounter significant delays in bringing our product candidates to market and be precluded from manufacturing or selling our product candidates, any of which could harm our business significantly. The cost of maintaining our patent protection globally is high and requires continuous review and compliance. We may not be able to effectively maintain our intellectual property position throughout the major markets of the world. The USPTO and foreign patent authorities require maintenance fees, payments and continued compliance with a number of procedural and documentary requirements. Noncompliance may result in abandonment or lapse of patents or patent applications and a partial or complete loss of patent rights in the relevant jurisdiction. Such a loss could reduce royalty payments for lack of patent coverage from our collaboration partners or may result in competition, either of which could have a material adverse effect on our business. We have made, and will continue to make, certain strategic decisions in balancing the costs and the potential protections afforded by the patent laws of certain countries. As a result, we may not be able to prevent third parties from practicing our inventions in all countries, or from selling or importing products made using our inventions in and into the United States or other countries. Third parties may use our technologies in territories in which we have not obtained patent protection to develop their own products and may infringe our patents in territories which provide inadequate enforcement mechanisms. Such third- party products may compete with our product candidates, and our patents or other intellectual property

rights may not be effective or sufficient to prevent them from competing. Such competition could materially and adversely affect our business and financial condition. Intellectual property rights do not address all potential threats to any competitive advantage we may have. The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and intellectual property rights may not adequately protect our business or permit us to maintain our competitive advantage. The following examples are illustrative: • Others may be able to make compounds that are the same as, or similar to, our current or future product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed. • We or any of our licensors or strategic partners might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or have exclusively licensed. • We or any of our licensors or strategic partners might not have been the first to file patent applications covering certain of our inventions. • Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights. • The prosecution of our pending patent applications may not result in granted patents. • Granted patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, because of legal challenges by our competitors. • Patent protection on our product candidates may expire before we are able to develop and commercialize the product, or before we are able to recover our investment in the product. • Our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for such activities, as well as in countries in which we do not have patent rights and may then use the information learned from such activities to develop competitive products for sale in markets where we intend to market our product candidates. Risks Related to Our Common Stock **The price of our common stock might fluctuate significantly, and you could lose all or part of your investment. The price of our common stock fluctuates widely. Continued volatility in the market price of our common stock might prevent a stockholder from being able to sell shares of our common stock at or above the price paid for such shares. The trading price of our common stock may continue to be volatile and subject to wide price fluctuations in response to various factors, many of which are beyond our control, such as the progress, results and timing of our clinical and nonclinical studies and other studies involving our product candidates, the success or failure of our product candidates, the receipt or loss of required regulatory approvals for our product candidates, the availability of capital or the other risks discussed in this " Risk Factors " section.** Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware will be 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 bring a claim in a judicial forum they find favorable for disputes with us or our directors, officers or other employees. Our amended and restated bylaws provide that, with certain limited exceptions, unless we consent to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of fiduciary duty owed by any of our current or former directors, officers or other employees to us or to our stockholders; (3) any action asserting a claim arising pursuant to the Delaware General Corporation Law, or our certificate of incorporation or bylaws (as each may be amended from time to time); or (4) any action asserting a claim governed by the internal affairs doctrine. Alternatively, if such court does not have jurisdiction, the Superior Court of Delaware, or, if such other court does not have jurisdiction, the United States District Court for the District of Delaware, will be the sole and exclusive forum for such actions and proceedings. The choice of forum provision may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and other employees. Alternatively, if a court were to find the choice of forum provision contained in our amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could have a material adverse impact on our business. The choice of forum provision in our amended and restated bylaws will not preclude or contract the scope of exclusive federal or concurrent jurisdiction for actions brought under the federal securities laws, including the Exchange Act or the Securities Act, or the respective rules and regulations promulgated thereunder. ~~The price of our common stock might fluctuate significantly, and you could lose all or part of your investment. The price of our common stock fluctuates widely. Continued volatility in the market price of our common stock might prevent a stockholder from being able to sell shares of our common stock at or above the price paid for such shares. The trading price of our common stock may continue to be volatile and subject to wide price fluctuations in response to various factors, many of which are beyond our control, such as the progress, results and timing of our clinical and nonclinical studies and other studies involving our product candidates, the success or failure of our product candidates, the receipt or loss of required regulatory approvals for our product candidates, the availability of capital or the other risks discussed in this " Risk Factors " section.~~