Risk Factors Comparison 2024-02-29 to 2023-03-02 Form: 10-K

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

~~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 in this annual report on Form 10- K, including our consolidated financial statements and related notes and " Management' s Discussion and Analysis of Financial Condition and Results of Operations, " before investing in our common stock.~~ The **following summarizes** ~~risks and uncertainties described below are not~~ the **principal** ~~only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important~~ factors that **make** ~~affect us. If any~~ **an** ~~of~~ **investment in** the **Company speculative** ~~following risks occur, our~~ **or** ~~business~~ **risky** , ~~operating results and prospects could be materially harmed. In that event, the price of our common stock could decline, and you could lose part or~~ all of ~~your investment. Summary~~ **which are more fully described in the** Risk Factors ~~Our business is subject to a number of risks and uncertainties, including those highlighted in the~~ section ~~titled "~~ **below. This summary should be read in conjunction with the** Risk Factors ~~" immediately following this~~ **section and should not be relied upon as an exhaustive** summary **of the material risks facing our business** . ~~Some~~ **The occurrence of any** of these risks ~~are: • We~~ **, could harm our business, financial condition, results of operations** and **/** ~~our~~ **or** ~~independent auditors~~ **growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we** have **made** ~~expressed substantial doubt about our ability to continue as a going concern. • We will need substantial additional funding. If we are unable to raise capital when needed, we would be compelled to delay, reduce or eliminate our product development programs or commercialization efforts. • We depend heavily on the success of our most advanced product candidates, pegtarviliase and pegzilarginase. Existing and future clinical trials of our product candidates, including pegtarviliase and pegzilarginase may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed. • The results from our global pivotal PEACE Phase 3 trial may not support marketing approval, and the FDA or other regulatory authorities may require us to conduct additional clinical trials or evaluate current subjects for an additional follow- up period. • Clinical drug development involves a lengthy and expensive process with an uncertain outcome. We may experience delays in completing, or ultimately be unable to complete, the development and commercialization of any of our product candidates. • Our engineered human enzyme product candidates represent a novel therapeutic approach, which could result in heightened regulatory scrutiny, delays in clinical development, or delays in our ability to achieve regulatory approval or commercialization of our product candidates. • We have only initiated clinical trials for pegtarviliase and pegzilarginase for the treatment of certain conditions. We have not dosed any of our other product candidates in humans. Our existing and future planned clinical trials may reveal significant adverse events, toxicities or other side effects not seen in our nonclinical studies or early stage clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates. • Delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials could delay or prevent our receipt of necessary regulatory approvals. • We contract with third parties for the manufacture of our product candidates for nonclinical studies and our ongoing and future planned clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates at an acceptable cost and quality, which could delay, prevent or impair our development or commercialization efforts. • If there are delays in obtaining, or we are not able to obtain, required regulatory approvals in the United States or in foreign jurisdictions, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired. • If we are unable to obtain and maintain intellectual property protection for our technology and product candidates, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and product candidates similar or identical to ours, and our ability to successfully commercialize our technology and product candidates may be impaired. • The outbreak of the novel strain of coronavirus, SARS- CoV- 2 and its emerging variants, which causes COVID- 19, has, and may continue to, adversely impact our business, including supply chain interruptions. Risks Related to Our Financial Position and Need for Additional Capital The Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company' s ability to continue as a going concern within one year after the date the financial statements included~~ in this Annual Report on Form 10- K **and those we may make from time to time. You should consider all of the risk factors described in our public filings when evaluating our business. Risk Factor Summary Risks Related to Our Financial Condition and Capital Requirements • We will not be able to continue as a going concern if we** are **unable** ~~issued. Based upon the Company' s current operating plans, the Company believes that it has sufficient resources to fund operations into the fourth quarter of 2023 with its existing cash, cash equivalents, and marketable securities. Accordingly, based on its recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need~~ to raise additional capital **when needed. • We have never generated any revenue from product sales and may never be profitable. • We anticipate that we will continue** to ~~finance~~ **incur significant losses for the foreseeable future. • We may not be able to raise the capital that we need to support our business plans and raising additional capital may cause dilution to our stockholders and restrict our operations. Risks Related to the Discovery, Development and Commercialization • We face competition from companies that have developed or may develop competing programs. • Our programs are in preclinical stages of development and may fail in development or suffer delays. • We are substantially dependent on the success of the SPY001 and SPY002 programs. • We may fail to achieve our projected development goals in the time frames we announce and expect. • Any drug delivery device potentially used may have** its

own regulatory development, supply, and other risks. • We may not be successful in our efforts to build a pipeline of product candidates with commercial value. • Our studies and trials may not be sufficient to support regulatory approval of any of our product candidates. • If we are unable to successfully develop complementary diagnostics for our therapeutic product candidates, we may not realize their full commercial potential. • We have limited experience in developing and commercializing diagnostics and have never applied for or obtained regulatory clearance or approval for any diagnostic tests. • Additional time may be required to obtain regulatory approval for our product candidates and future **product candidates because of their status as combination products. • We may encounter difficulties enrolling participants in our future clinical trials. • Preliminary or " topline " data from our clinical trials may change as more data becomes available. • Our future clinical trials may reveal significant adverse events or side effects. • We may fail to capitalize on more profitable or potentially successful product candidates than those we pursue. • Any of our future approved products may not achieve regulatory approval, market acceptance or commercial success. • Certain of our programs may compete with our other programs. • The FDA may not accept data from clinical trials we conduct at sites outside the United States. Risks Related to Government Regulation • FDA and comparable foreign regulatory approval processes are lengthy and time- consuming and we may not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates. • We may not be able to meet requirements for chemistry, manufacturing and control of our programs. • Our product candidates may face competition sooner than anticipated based on rules and regulations that may apply or government decisions with respect to our intellectual property. • Even if we receive regulatory approval, we will be subject to extensive ongoing regulatory obligations. • We may face difficulties from healthcare legislative reform measures. • Our** operations ~~,~~ **and arrangements with third- parties are subject to healthcare regulatory laws. • We may be unable to offer products at competitive prices due to unfavorable pricing regulations and / or third- party coverage and reimbursement policies. • We may face criminal liability or ~~the~~ other ~~Company determined~~ consequences for violations of U. S. and foreign trade regulations. • Foreign governments may impose strict price controls, which may adversely affect our revenue. • Any accelerated review designations (e. g. fast track designation) we may pursue may not hasten development or regulatory review. Risks Related to Our Intellectual Property • Our ability to obtain and protect our patents and other proprietary rights is uncertain. • We may fail in obtaining or maintaining necessary rights to our programs. • We may be subject to patent infringement claims or may need to file such claims. • We may be subject to claims of wrongful hiring of employees or wrongful use of confidential information. • Our patents and our ability to protect our products may be impaired by changes to patent laws. • Our patent protection could be reduced or eliminated for non- compliance with regulatory requirements. • We may fail to identify or interpret relevant third- party patents. • We may become subject to claims challenging the inventorship or ownership of our intellectual property. • Patent terms may be inadequate to protect our competitive position of our programs. • Our technology licensed from various third parties may be subject to retained rights. Risks Related to Our Reliance on Third Parties • We may fail to maintain collaborations and licensing arrangements with third parties** that **we rely on. • Third- parties we rely on for the execution of preclinical studies and clinical trials may fail to carry out ~~there~~ their contractual duties. • We may be unable to use third- party manufacturing sites or our third- party manufacturers may encounter difficulties in production. Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business • We may experience difficulties in managing the growth of our organization. • We may fail to attract or retain highly qualified personnel. • Our ability to operate in foreign markets** is ~~substantial doubt about~~ **subject to regulatory burdens, risks and uncertainties. • Our estimates of market opportunity and forecasts of market growth may be inaccurate and our business may not grow at similar rates, or at all. • Our employees or third- parties may engage in misconduct or ~~the~~ other improper activities. • We may be impacted by security or data breaches or other improper access to our data. • Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited. • We may fail to comply with privacy and data security regulations. • We may fail to comply with environmental, health and safety laws and regulations. • We may be subject to adverse legislative or regulatory tax changes. • We may fail to realize the benefits of our business or product acquisitions or our strategic alliances. • We may be impacted by the failure of financial institutions. Risks Related to Our Common Stock • We may fail to obtain stockholder approval of the conversion of our Series B Preferred Stock. • Our certificate of incorporation, Delaware law and certain contracts include anti- takeover provisions. • Our certificate of incorporation and bylaws contain exclusive forum provisions. • We do not anticipate paying any dividends in the foreseeable future. • Future sales of shares by existing stockholders could cause our stock price to decline. • Future sales and issuances of equity and debt could result in additional dilution to our stockholders. • Our principal stockholders own a significant percentage of our stock. General Risk Factors • The market price of our common stock has historically been volatile and may drop in the future. • We incur significant costs associated with complying with public ~~Company~~ company reporting requirements. • A lack of analyst coverage may cause a decline in our stock price or trading volume. • We may fail to maintain proper and effective internal controls. We will need to raise additional capital, and if we are unable to do so when needed, we will not be able to continue as a going concern. This Annual Report includes disclosures regarding our management** ' s **assessment of our** ability to continue as a going concern **. As ~~within twelve months~~** of ~~the issuance date~~ **December 31, 2023, we had $ 339. 6 million** of **cash, cash equivalents, marketable securities, and restricted cash. We will need to raise additional capital to continue to fund our operations and service our debt obligations in ~~these~~ the future ~~financial statements~~. ~~In view of these matters~~ If we are unable to raise additional capital when needed , ~~our ability~~ we will not be able** to continue as a going concern **. Developing our product candidates requires a substantial amount of capital. We expect our research and development expenses to increase in connection with our ongoing activities, particularly as we advance our product candidates through clinical trials. We will need to raise additional capital to fund our operations and such funding may not be available to us on acceptable terms,**

or at all, and such funding may become even more difficult to obtain due to rising interest rates and the current downturn in the U. S. capital markets and the biotechnology sector in general. Competition for additional capital among biotechnology companies may be particularly intense during this present economic downturn. We may be unable to raise capital through public offerings of our common stock and may need to turn to alternative financing arrangements. Such arrangements, if we pursue them, could involve issuances of one or more types of securities, including common stock, Preferred Stock, convertible debt, warrants to acquire common stock or other securities. These securities could be issued at or below the then prevailing market price for our common stock. In addition, if we issue debt securities, the holders of the debt would have a claim to our assets that would be superior to the rights of stockholders until the principal, accrued and unpaid interest and any premium or make- whole has been paid. Interest on any newly- issued debt securities and / or newly- incurred borrowings would increase our operating costs and reduce our net income (or increase our net loss), and these impacts may be material. If the issuance of new securities results in diminished rights to holders of our common stock, the market price of our common stock could be materially and adversely affected. We do not currently have any products approved for sale and do not generate any revenue from product sales. Accordingly, we expect to rely primarily on equity and / or debt financings to fund our continued operations. Our ability to raise additional funds will depend, in part, on the success of our preclinical studies and clinical trials and other product development activities, regulatory events, our ability to identify and enter into licensing or other strategic arrangements, and other events or conditions that may affect our value or prospects, as well as factors related to financial, economic and market conditions, many of which are beyond our control. There can be no assurances that sufficient funds will be available to us when required or on acceptable terms, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to: • significantly delay, scale back, or discontinue the development or commercialization of our product candidates; • seek strategic partnerships, or amend existing partnerships, for research and development programs at an earlier stage than otherwise would be desirable or that we otherwise would have sought to develop independently, or on terms that are less favorable than might otherwise be available in the future; • dispose of technology assets, or relinquish or license on unfavorable terms, our rights to technologies or any of our product candidates that we otherwise would seek to develop or commercialize ourselves; • pursue the sale of our company to a third party at a price that may result in a loss on investment for our stockholders; or • file for bankruptcy or cease operations altogether (and face any related legal proceedings). Any of these events could have a material adverse effect on our business, operating results and prospects. Even if successful in raising new capital, we could be limited in the amount of capital we raise due to investor demand restrictions placed on the amount of capital we raise or other reasons. Additionally, any capital raising efforts are subject to significant risks and contingencies, as described in more detail under the risk factor titled " Raising additional capital may cause dilution to our stockholders, restrict our operations, or require us to relinquish rights. " We have no products approved for commercialization and have never generated any revenue from product sales. Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic collaborators, to successfully complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating revenue from product sales for the foreseeable future. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to: • completing research and development of our product candidates; • obtaining regulatory and marketing approvals for our product candidates for which we complete clinical trials; • manufacturing product candidates and establishing and maintaining supply and manufacturing relationships with third parties that are commercially feasible, meet regulatory requirements and our supply needs in sufficient quantities to meet market demand for our product candidates, if approved; • qualify for adequate coverage and reimbursement by government and third- party payors for any product candidates for which we obtain regulatory and marketing approval; • marketing, launching, and commercializing product candidates for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor; • gaining market acceptance of our product candidates as treatment options; • addressing any competing products and technological and market developments; • implementing internal systems and infrastructure, as needed; • protecting and enforcing our intellectual property rights, including patents, trade secrets, and know- how; • negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter; • obtaining coverage and adequate reimbursement from third- party payors and maintaining pricing for our product candidates that supports profitability; and • attracting, hiring, and retaining qualified personnel. Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by regulatory authorities to perform clinical and other studies in addition to those that we anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Portions of the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement may be in- licensed from third parties, which make the commercial sale of such in- licensed products potentially subject to additional royalty and milestone payments to such third parties. We will also have to develop or acquire manufacturing capabilities or continue to contract with contract manufacturers in order to continue development and potential commercialization of our product candidates. For instance, if the costs of manufacturing our drug product are not commercially feasible, we will need to develop or procure our drug product in a commercially feasible manner in order to successfully commercialize a future approved product, if any. Additionally, if we are not able to generate revenue from the sale of any approved products, we may never become profitable. We have historically

incurred losses, have a limited operating history on which to assess our business, and anticipate that we will continue to incur significant losses for the foreseeable future. We are a biopharmaceutical company with a limited operating history. Since inception, we have incurred significant operating losses. For the years ended December 31, 2023, 2022 and 2021, we reported a net loss of $ 338. 8 million, $ 83. 8 million and $ 65. 8 million, respectively. As of December 31, 2023, we had an accumulated deficit of $ 764. 4 million. We will need to raise substantial additional capital to continue to fund our operations in the future. If our stockholders do not timely approve the conversion of our Series B Preferred Stock, then the holders of our Series B Preferred Stock may be entitled to require us to settle their shares of Series B Preferred Stock for cash at a price per underlying share of common stock equal to the last reported closing sale price of common stock on the principal trading market on which the common stock is listed as of the trading day immediately prior to the date on which a request to convert shares of Series B Preferred Stock into shares of common stock is delivered to us by a holder in accordance with the terms of the Series B Certificate of Designation and we fail to deliver such shares of common stock, as described in our Series B Certificate of Designation relating to the Series B Preferred Stock. Because the specific timing of the exercise of the cash redemption is not under our control and is dependent **the closing sale price of our common stock at the time of such conversion, we cannot quantify the aggregate amount of the potential cash settlement; however, for illustrative purposes only, if all of our holders of Series B Preferred Stock had delivered requests to convert their shares of Series B Preferred Stock on February 26, 2024 and assuming we were obligated to settle such conversions in cash pursuant to the terms of the Series B Certificate of Designation, a total of $ 141, 480, 000 would have been payable to such holders as a result of the cash settlement of all 6, 000, 000 shares of common stock issuable** upon **the conversion of 150, 000 shares of Series B Preferred Stock, at a price of $ 23. 58 per share of common stock, which was the closing sale price of our common stock on the Nasdaq Global Select Market on February 23, 2024. Failure to raise capital as and when needed, on favorable terms or at all, would have a negative impact on our financial condition and** our ability to **develop our product candidates. Changing circumstances may cause us to consume capital significantly faster or slower than we currently anticipate. If we are unable to acquire additional capital or resources, we will be required to modify our operational plans to complete future milestones and we may be required to delay, limit, reduce or eliminate development or future commercialization efforts of product candidates and / or programs. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available financial resources sooner than we currently anticipate. We may be forced to reduce our operating expenses and raise additional funds to meet our working capital needs, principally through the additional sales of our securities or debt financings or entering into strategic collaborations. We have devoted substantially all of our financial resources to identify, acquire, and develop our product candidates, including conducting preclinical and clinical development of the legacy rare disease clinical studies conducted by us prior to the Asset Acquisition (the" Legacy Pipeline") and the preclinical development of our current IBD pipeline, and providing general and administrative support for our operations. To date, we have funded our operations primarily from the sale and issuance of convertible preferred and common equity securities, pre- funded warrants, the collection of grant proceeds, and the licensing of our product rights for commercialization of pegzilarginase in Europe and certain countries in the Middle East. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations, or grants. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We expect our losses to increase as our product candidates enter more advanced clinical trials. It may be several years, if ever, before we complete pivotal clinical trials or have a product candidate approved for commercialization. We expect to invest significant funds into the research and development of our current product candidates to determine the potential to advance these product candidates to regulatory approval. If we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, coverage and adequate reimbursement from third- party payors, and adequate market share for our product candidates in those markets. Even if we obtain adequate market share for our product candidates, because the potential markets in which our product candidates may ultimately receive regulatory approval could be very small, we may never become profitable despite obtaining such market share and acceptance of our products. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future and our expenses will increase substantially if and as we: • continue the preclinical development and initiate the clinical development of our product candidates; • continue efforts to discover and develop new product candidates; • continue the manufacturing of our product candidates or increase volumes manufactured by third parties; • advance our product candidates into larger, more expensive clinical trials; • initiate additional preclinical studies or clinical trials for our product candidates; • seek regulatory and marketing approvals and reimbursement for our product candidates; • establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval and market for ourselves; • seek to identify, assess, acquire, and / or develop other product candidates; • make milestone, royalty, or other payments under third- party license agreements; • seek to maintain, protect, and expand our intellectual property portfolio; • pay penalties under our registration rights agreement for failing to timely register the applicable securities; • seek to attract and retain skilled personnel; and • experience any delays or encounter issues with the development and potential for regulatory approval of our clinical and product candidates such as safety issues, manufacturing delays, clinical trial accrual delays, longer follow- up for planned studies or trials, additional major studies or trials, or supportive trials necessary to support marketing approval. Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period- to- period comparison of our results of operations may not be a good indication of our future performance. Until such time, if ever, as we can generate substantial revenue from the**

sale of our product candidates, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and development agreements. To the extent that we raise additional capital through ~~outside sources~~ **the sale of equity securities or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of common stock. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements with third parties when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to third parties to develop and market product candidates that we would otherwise prefer to develop and market ourselves. To the extent that we raise additional capital through the sale of equity, including pursuant to any sales under convertible debt or other securities convertible into equity, the ownership interest of our stockholders will be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect the rights of our stockholders. For instance, in December 2023, we sold an aggregate of 6, 000, 000 shares of common stock and 150, 000 shares of our Series B Preferred Stock in the December 2023 PIPE to the December 2023 Investors for gross proceeds of $ 180. 0 million. Subject to receiving the requisite stockholder approval and certain beneficial ownership limitations set by each holder of Series B Preferred Stock, each share of Series B Preferred Stock will automatically convert into an aggregate of 40 shares of our common stock** . We ~~intend~~ **are required to solicit the consent of our stockholders with regard to conversion of the shares of our Series B Preferred Stock which will be voted on at our 2024 annual meeting of stockholders. If our stockholders fail to approve such matters, we may be subject to financial penalties that could materially harm our business, including the forced settlement of shares of Series B Preferred Stock for cash, as described in our Series B Certificate of Designation. Debt financing, if available, would likely involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, making additional product acquisitions, or declaring dividends. If we raise additional funds through strategic collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates or future revenue streams or grant licenses on terms that are not favorable to us. We cannot be assured that we will be able to obtain additional funding if and when necessary to fund our entire portfolio of product candidates to meet our projected plans. If we are unable** to obtain funding **on a timely basis, we may be required to delay or discontinue one or more of our development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on potential business opportunities, which could materially harm our business, financial condition, and results of operations. Risks Related to Discovery, Development and Commercialization We face competition from entities that have developed or may develop programs for the diseases addressed by our product candidates. The development and commercialization of drugs is highly competitive. Our product candidates, if approved, will face significant competition and our failure to effectively compete may prevent us from achieving significant market penetration. We compete with a variety of multinational biopharmaceutical companies, specialized biotechnology companies and emerging biotechnology companies, as well as academic institutions, governmental agencies, and public and private research institutions, among others. Many of the companies with which we are currently competing or will complete against in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, clinical trial conduct, regulatory approvals, and marketing than we do. Mergers and acquisitions in the pharmaceutical and biotechnology 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, establishing clinical trial sites, recruiting participants for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our product candidates. Our competitors have developed, are developing or will develop programs and processes competitive with our programs and processes. Competitive therapeutic treatments include** ~~the~~ **those** ~~sale of common stock in public offerings~~ **that have already been approved and accepted by the medical community and any new treatments. Our success will depend partially on our ability to develop and commercialize products that have a competitive safety, efficacy, dosing** and / or ~~private placements~~ **presentation profile. Our commercial opportunity and success will be reduced or eliminated if competing products are safer** , ~~debt financings~~ **more effective** , **have a more attractive dosing profile or presentation or are less expensive than the products we develop, or if** ~~or~~ **our** ~~through~~ **competitors develop competing products or if biosimilars enter the market more quickly than we do and are able to gain market acceptance. See the section titled " Business – Competition " for more discussion about our competitors. In addition, because of the competitive landscape for inflammatory and immunology (" I & I") indications, we may also face competition for clinical trial enrollment. Clinical trial enrollment will depend on many factors, including if potential clinical trial participants choose to undergo treatment with approved products or enroll in competitors' ongoing clinical trials for programs that are under development for the same indications as our programs. An increase in the number of approved products for the indications we are targeting with our programs may further exacerbate this competition. Our inability to enroll a sufficient number of participants could, among** other **things** ~~capital sources~~ , **delay** ~~including collaborations with other companies or~~ **our development timeline, which may further harm** ~~other strategic transactions. The failure to obtain sufficient financing or~~ **our** ~~strategic partnerships could~~ **competitive position. Our**

product candidates are in preclinical stages of development and may fail in development or suffer delays that materially and adversely affect ~~our~~ **their commercial** ~~ability~~ **viability** ~~to achieve~~ **. If we** ~~our~~ **or our current** ~~business objectives and continue as a going concern. Our limited operating history may make it difficult for~~ **or** ~~you to evaluate the success of our business to date and to assess our~~ future **collaborators** ~~viability. We~~ are **unable** ~~a clinical- stage biotechnology company. We began operations as a limited liability company in December 2013 and converted~~ to **complete development of,** ~~a Delaware corporation in March 2015. Our operations to date have been limited to organizing and staffing our~~ **or commercialize** ~~company, business planning, raising capital, acquiring and developing~~ our ~~technology, identifying potential~~ product candidates, ~~undertaking nonclinical studies, and preparing for~~ **or experience significant delays in doing so** , ~~commencing and conducting clinical trials of~~ our ~~most advanced~~ **business will be materially harmed. We have no products on the market, and all of our** product candidates **are in preclinical stages** ~~, pegtarviliase and pegzilarginase. Other than the PEACE Phase 3 trial~~ of **development and** ~~pegzilarginase, we~~ have not ~~demonstrated our~~ **been tested in humans. As a result, we expect it will be many years before we commercialize any product candidate, if ever. Our** ability to **achieve and sustain profitability depends on obtaining regulatory approvals for, and** successfully ~~complete a pivotal clinical trial~~ **commercializing, our product candidates, either alone or with third parties, and we cannot guarantee you that we will ever obtain regulatory approval for any of our product candidates** . We have not yet demonstrated our ability to ~~successfully~~ **initiate or complete any clinical trials,** obtain ~~marketing~~ **regulatory** approvals, manufacture a **clinical or** commercial scale product or arrange for a third party to do so on our behalf ~~, other than for pegtarviliase and pegzilarginase~~ , or conduct sales and marketing activities necessary for successful product commercialization. **Before** ~~Products, on average, take 10 to 15 years to be developed from the time they are discovered to the time they are approved and available for treating patients. Although we have recruited a team that has experience with clinical trials, as a company we have limited experience in conducting clinical trials. Due to this limited experience, we cannot be certain that planned or ongoing clinical trials will begin or be completed on time, if at all, and / or will yield clinical results that we may expect. Consequently, any predictions you make about our future success or viability based on our short operating history to date may not be as accurate as they could be if we had a longer operating history or an established track record in conducting clinical trials or commercializing products. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. In the future, we will need to transition from a company with a research focus to a company also capable of supporting commercial activities. We may not be successful in such a transition. We have no source of product revenue and we have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability. We have a limited operating history and no approved products. Our ability to generate revenue and become profitable depends upon our ability to successfully complete the development of any of our product candidates, including pegtarviliase and pegzilarginase, for any of our target indications and to obtain~~ **obtaining** ~~necessary regulatory approvals. To date, we have recognized revenue from a license and supply agreement and a fully utilized government grant and have not generated any product revenue. Even if we receive~~ regulatory approval for ~~any~~ **the commercial distribution** of our product candidates, we ~~do not know when~~ **or an existing or future collaborator must conduct extensive preclinical tests and clinical trials to demonstrate** ~~these~~ -- **the safety and efficacy in humans of our programs and future** product candidates ~~will generate revenue~~ **. We or our collaborators may experience delays in initiating or completing clinical trials. We or our collaborators also may experience numerous unforeseen events during, or as a result of, any current or future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our current product candidates or any future product candidates, including: • regulators or institutional review boards (" IRBs "), the FDA or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site; • we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations (" CROs "), the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites; • clinical trial sites deviating from trial protocol or dropping out of a trial; • clinical trials of any product candidates may fail to show safety or efficacy, produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs; • the number of subjects required** for **clinical trials of any product candidates may be larger than we anticipate, especially if regulatory bodies require completion of non- inferiority or superiority trials, enrollment in these clinical trials may be slower than we anticipate or subjects may drop out of these clinical trials or fail to return for post- treatment follow- up at a higher rate than we anticipate; • our third- party contractors may fail to comply with regulatory requirements or meet their contractual obligations to** us **in a timely manner** , ~~if~~ **or** at all ~~. In addition , since inception, we have incurred significant operating losses. For~~ **or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators; • we may elect to, or regulators, IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants in our trials are being exposed to unacceptable health risks; • the cost of clinical trials of any of our programs may be greater than we anticipate; • the quality of our product candidates or** ~~the~~ **other** ~~years ended December 31, 2022 and 2021, we~~ **materials necessary to conduct clinical trials of our product candidates may be inadequate to initiate or complete a given clinical trial; • our inability to manufacture sufficient quantities of our product candidates for use in clinical trials; •** ~~reported~~ **reports** ~~a net loss~~ **from clinical testing** of **other therapies may raise safety or efficacy concerns about our programs; • our failure to establish** ~~$ 83. 8 million and $ 65. 8 million, respectively. As of December 31, 2022, we had~~ an **appropriate safety profile for a product candidate** ~~accumulated deficit of $ 425. 6 million. Based upon our current operating plans, we believe that we have sufficient resources to fund operations into the fourth quarter of 2023 with our existing cash, cash equivalents, and marketable securities. Accordingly,~~

based on **clinical** ~~recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our~~ **or preclinical** ~~future operations, we determined that there is substantial doubt about our ability to continue as a going concern within twelve months of the issuance date~~ **data** ~~of the financial statements included in this Annual Report on Form 10- K. We plan to address this condition through the sale of common stock in public offerings and / or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions. In the past, we have financed our operations primarily through private placements of our preferred stock, the initial public offering of our common stock, follow- on public offerings of our common stock and pre-funded warrants, collection of a research grant, and the licensing of our product rights~~ for **such** ~~commercialization of pegzilarginase in Europe and several countries in the Middle East. We have devoted substantially all of our efforts to research and development. Currently, we are conducting clinical development for pegtarviliase for the treatment of Homocystinuria and pegzilarginase for the treatment of Arginase 1 Deficiency. We have not initiated clinical development of our other~~ product candidates **as well as data emerging** ~~and none of our product candidates are ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, and the net losses we incur may fluctuate significantly~~ from **other therapies in the same class** ~~quarter to quarter. We anticipate that our expenses will increase substantially if and~~ as ~~we: • continue our research, nonclinical development and clinical development of~~ our product candidates; **and** ~~• seek~~ **the FDA or other regulatory authorities may require us** to ~~identify~~ **submit** additional **data such as long- term toxicology studies, or impose other requirements before permitting us to initiate a clinical trial. Commencing clinical trials in the United States is subject to acceptance by the FDA of an IND, BLA or similar application and finalizing the trial design based on discussions with the FDA and other regulatory authorities. In the event that the FDA requires us to complete additional preclinical studies or we are required to satisfy other FDA requests prior to commencing clinical trials, the start of our first clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials, delay the enrollment of our clinical trials or impose stricter approval conditions than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the EU. We may not have the financial resources to continue development of, or to modify existing or enter into new collaborations for, a product candidate if we experience any issues that delay or prevent regulatory approval of, or our ability to commercialize, our** product candidates ~~; • conduct additional nonclinical studies~~ **. We or our current or future collaborators' inability to complete development of, or commercialize our product candidates, or significant delays in doing so, could have a material** and ~~initiate~~ **adverse effect on our business, financial condition, results of operations and prospects. We are substantially dependent on the success of our two most advanced programs, SPY001 and SPY002, and our anticipated** clinical trials ~~for our product candidates; • seek marketing approvals for any~~ of ~~our product candidates that~~ **such programs may not be** ~~successfully~~ -- **successful** ~~complete clinical trials, including pivotal trials; • establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval; • maintain, expand and protect our intellectual property portfolio; • hire additional executive, clinical, quality control and scientific personnel; • add operational, financial and management information systems and personnel, including personnel to support our product development; and • acquire or in- license other product candidates and technologies~~ . **Our future success** ~~We are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability because of the numerous risks and uncertainties associated with product development. In addition, our expenses could increase significantly beyond expectations if we are required by the FDA, EMA, MHRA, or other relevant regulatory authorities, or collectively, the Health Authorities, to modify protocols of our clinical trials or perform studies in addition to those that we currently anticipate. Even if pegzilarginase, or any of our other product candidates,~~ is **substantially dependent** ~~approved for commercial sale, we anticipate incurring significant costs associated with the commercial launch of any product candidate. To become and remain profitable, we must develop and eventually commercialize a product candidate or product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing nonclinical testing, initiating and completing clinical trials of one or more of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we obtain marketing approval and satisfying any post- marketing requirements. We may never succeed in these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. We reported in April 2022 that we submitted a BLA to the FDA for pegzilarginase for the treatment of Arginase 1 Deficiency and announced in June 2022 that we received a Refuse to File letter, or RTF Letter, from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. We are continuing to engage with FDA to identify a potential path to BLA resubmission. In October 2022, we received a letter from the FDA regarding a protocol amendment for our Phase 1 / 2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial~~ on ~~partial clinical hold for the enrollment of patients less than 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. We are in the nonclinical development stages for our remaining product candidates. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair~~ our ability to **timely** ~~raise capital, maintain or expand our research and development efforts, expand our business or continue our operations. We expect our expenses to increase in parallel with our ongoing activities, particularly~~

as we initiate and continue clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates , **and then successfully** we expect to incur significant commercialization **commercialize** expenses related **, our** to **two** product sales **most advanced programs** , **SPY001** marketing, manufacturing and distribution **SPY002** . **We exercised our Option** Furthermore, we expect to continue to incur additional costs associated with **respect** operating as a public company. Accordingly, we will need to **the SPY001** obtain substantial additional funding to support our continuing operations. If we are unable to raise capital when needed for any reason, including but not limited to inflation, increasing interest rates, volatile market conditions and **SPY002 programs** global events, or on acceptable terms **July 12** , **2023** we would be forced to delay, reduce or eliminate our discovery and **December 14** nonclinical development programs , **2023** our ongoing clinical development , **respectively** or any future clinical development or commercialization efforts. Our future capital requirements will depend on many factors, including: • the costs associated with the scope, progress and results of compound discovery, nonclinical development, laboratory testing and clinical trials for our product candidates; • the extent to which we enter into partnerships or other arrangements with third parties in order to further develop our product candidates; • the costs and fees associated with the discovery, acquisition or in- license of product candidates or technologies; • our ability to establish collaborations on favorable terms, if at all; • the costs of commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval; • revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval; and • the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property- related claims. Even if successful in raising new capital, we could be limited in the amount of capital we raise due to investor demand restrictions placed on the amount of capital we raise or other reasons. For example, as of the filing of this Annual Report, we are subject to the limitations set forth in Instruction I. B. 6 of Form S- 3 (the" baby shelf restrictions") or other reasons. If we are unable to raise sufficient amounts of capital it could similarly affect our progress and we could be forced to delay, reduce, or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts. Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products, none of which have been approved to date. Accordingly, we will continue to rely on additional financing to achieve our business objectives, which may not be available to us on acceptable terms, or at all. Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or equity- linked offerings, debt financings, grants from research organizations, collaborations, and license and development agreements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, or if existing holders of warrants exercise their rights to purchase common stock, your ownership interest will be diluted, and the terms of these securities may rank senior to our common stock and include liquidation or other preferences, covenants or other terms that adversely affect your rights as a common stockholder. Further, any future sales of our common stock by us or resale of our common stock by our existing stockholders could cause the market price of our common stock to decline. A decline in the value of our company would also cause you to lose part or even all of your investment. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and / or that may reduce the value of our common stock. Risks Related to Our Product Development and Regulatory Approval We may not be successful in advancing the clinical development of our product candidates, including pegtarviliase and pegzilarginase. In order to execute on our strategy of advancing the clinical development of our product candidates, we completed the global pivotal PEACE Phase 3 clinical trial and a Phase 1 / 2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency . We are **investing** conducting an open- label study of pegzilarginase for the treatment of Arginase 1 Deficiency, for patients that participated in our previous clinical trials, and a **majority** Phase 1 / 2 clinical trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. If our product candidates fail to work as we expect, or **our efforts** if we need to conduct additional studies to better understand the relationship between our product candidates and **financial resources into** clinical activity, (i. e. efficacy and safety), our ability to assess the **research and** therapeutic effect, seek regulatory approval or otherwise begin or further clinical development **of these programs** , could be compromised . We **anticipate initiating** announced on August 18, 2022 that a MAA for pegzilarginase for the treatment of Arginase 1 Deficiency has been submitted to and successfully validated by the EMA. The MAA was submitted by Immedica Pharma AB, our commercialization partner in Europe and the Middle East. Although we submitted our BLA to the FDA to support approval for pegzilarginase based on the results of PEACE Phase 3 trial, on June 2, 2022, we announced that we received a RTF Letter from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. The FDA has noted that, while the data presented in the PEACE Phase 3 trial overall appeared promising and hypothesis- generating, it disagreed that the efficacy results provide substantial evidence of effectiveness for pegzilarginase. The FDA also previously reiterated the need to generate evidence of effectiveness of the product candidate through an additional randomized placebo- controlled trial of a duration longer than 24 weeks given that efficacy data based on effort- dependent clinical outcome assessments and related endpoints have a high potential for bias. We may choose not to resubmit the BLA to the FDA. If we re- submit a BLA, the FDA may again decide not to file our BLA or approve the BLA in a timely manner, or at all. If the FDA does not file or approve our BLA, we may need to conduct additional studies and our expected timing of commercialization of pegzilarginase could be delayed, or we may never

~~commercialize pegzilarginase. We have in the past had to cease clinical development of a product candidate for another indication. For example, we discontinued clinical development of pegzilarginase for the treatment of the hematological malignancies acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, in December 2017 due to lack of evidence of clinical benefit. Additionally, we completed our~~ Phase 1 clinical trial **in healthy volunteers** of ~~pegzilarginase for~~ **SPY001 in** the ~~treatment~~ **first half** of ~~advanced solid tumors to study small cell lung cancer~~ **2024 and of SPY002 in the second half of 2024** , ~~uveal melanoma,~~ **each subject to the filing of** ~~and~~ **an IND** ~~cutaneous melanoma and our~~ **or foreign equivalent** ~~combination trial of pegzilarginase with pembrolizumab for the treatment of patients with SCLC. Such a discontinuation as in our prior oncology program may result in longer development times, larger trials~~ and ~~a greater likelihood of terminating the trial or not obtaining~~ regulatory approval. ~~We~~ **The success of our programs is** ~~depend~~ **dependent** ~~heavily~~ on ~~the success~~ **observing a longer half- life** of our ~~most advanced~~ product candidates ~~, pegtarviliase~~ **in humans than other mAbs currently marketed** and ~~pegzilarginase. Existing and future clinical trials of~~ **in development as we believe this longer half-life has the potential to result in a more favorable dosing schedule for** our product candidates, **assuming they** ~~including pegtarviliase and pegzilarginase, may not be successful~~ **successfully complete clinical development and obtain marketing approval** . ~~If~~ **This is based in part on the assumption that the longer half- life** we ~~are unable to commercialize~~ **have observed in non- human primates (" NHPs ") will translate into an extended half- life of** our product candidates **in humans. To the extent we do not observe this extended half- life when we dose humans with** ~~or~~ **our** ~~experience~~ **product candidates, it would** ~~significant~~ **significantly** ~~delays in doing so,~~ **and adversely affect the clinical and commercial potential of** our ~~business~~ **product candidates. Our programs** will **require additional** ~~be materially harmed. We have invested a significant portion of our efforts and financial resources in the nonclinical and~~ clinical development ~~and testing~~ **, evaluation** of **clinical, preclinical** ~~pegzilarginase for the treatment of patients with Arginase 1 Deficiency~~ and **manufacturing activities, product development, marketing approval** in ~~certain oncology trials~~ **multiple jurisdictions, substantial investment** and **significant marketing efforts before we** ~~pegtarviliase for the treatment of Homocystinuria. Our ability to~~ generate **any revenues from** product ~~revenues~~ **sales. We are not permitted to market or promote these programs** , ~~if~~ **or any other programs, before we receive marketing approval from the FDA and comparable foreign regulatory authorities, and we may** ~~ever~~ **never receive such marketing approvals** ~~, will depend heavily on the successful development and commercialization of pegtarviliase and pegzilarginase~~ . The success of ~~pegtarviliase, pegzilarginase, and~~ our ~~other~~ product candidates will depend on **a variety of factors. We do not have complete control over** many **of these** factors, including **certain aspects of clinical development and the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any current or future collaborator. Accordingly, we cannot assure you that we will ever be able to generate revenue through the sale of** ~~the~~ **these** ~~following: •~~ **product candidates, even if approved. If we are not successful in commercializing our SPY001 or SPY002 programs, or are significantly delayed in doing so, our business will be materially harmed. If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our product candidates may be delayed and our expenses may increase and, as a result, our stock price may decline. From time to time, we estimate the timing of the anticipated accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials, such as the expected timing for the anticipated commencement of our Phase 1 study, clinical trials in IBD, as well as the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are and will be based on numerous assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, or at all, the commercialization of our product candidates may be delayed or never achieved and, as a result, our stock price may decline. Additionally, delays relative to our projected timelines are likely to cause overall expenses to increase, which may require us to raise additional capital sooner than expected and prior to achieving targeted development milestones. Any drug delivery device that we potentially use to deliver our product candidates may have its own regulatory, development, supply and other risks. We expect to deliver our product candidates via a drug delivery device, such as an injector or other delivery system. There may be unforeseen technical complications related to the development activities required to bring such a product to market, including primary container compatibility and / or dose volume requirements. Our product candidates may not be approved or may be substantially delayed in** receiving ~~required~~ **approval if the devices that we choose to develop do not gain and / or maintain their own** regulatory approvals ~~for~~ **or** ~~the development and commercialization~~ **clearances. Where approval** of ~~our~~ **the drug** product ~~candidates as monotherapy or in combination with~~ **and device is sought under a single application,** ~~other~~ **the** ~~products; • establishing commercial manufacturing capabilities or making arrangements with~~ **increased complexity of the review process may delay approval. In addition, some drug delivery devices are provided by single- source unaffiliated** third- party **companies. We may be dependent** ~~manufacturers; • obtaining and maintaining patent and trade secret protection and non~~ **on** ~~patent exclusivity for our product candidates and their~~ **the sustained** ~~components; • enforcing and defending intellectual property rights and claims; • achieving desirable therapeutic properties for our product candidates' intended indications; • launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration~~ **cooperation** ~~with third parties; • acceptance of our product candidates, if~~ and **effort of** ~~when approved, by patients, the~~ **those** ~~medical community and~~ third- party ~~payors; • effectively competing with~~ **companies both to supply the devices and, in some cases, to conduct the studies required for approval or** other ~~therapies; and •~~ **regulatory clearance of the devices. Even if approval is obtained, we may also be dependent on those third- party companies continuing to** ~~maintaining~~ **maintain such approvals** ~~an acceptable safety profile of our~~ **or clearances once they have been received. Failure of third- party companies to supply the devices, to successfully complete studies on the devices in a timely manner, or to obtain or**

maintain required approvals or clearances of the devices could result in increased development costs, delays in or failure to obtain regulatory approval and delays in product candidates ~~through~~ **reaching the market or in gaining approval or clearance for expanded labels for new indications. Our approach to the discovery and development of our programs is unproven, and we may not be successful in our efforts to build a pipeline of programs with commercial value. Our approach to the discovery and development of the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement leverages clinically validated mechanisms of action and incorporates advanced antibody engineering to optimize half- life and other properties designed to overcome limitations of existing therapies. Our programs are purposefully designed to improve upon existing product candidates and products while maintaining the same, well- established mechanisms of action. However, the scientific research that forms the basis of our efforts to develop programs using half- life extension technologies, including YTE and LS amino acid substitutions, is ongoing and may not result in viable programs. We have limited clinical data on product candidates utilizing YTE and LS half- life extension technologies, especially in I & I indications, demonstrating whether they are safe or effective for long- term treatment in humans. The long- term safety and efficacy of these technologies and the extended half- life and exposure profile of our programs compared to currently approved products is unknown. We may ultimately discover that utilizing half- life extension technologies for our specific targets and indications and any programs resulting therefrom do not possess certain properties required for therapeutic effectiveness. We currently have only preclinical data regarding the increased half- life properties of our programs and the same results may not be seen in humans. In addition, programs using half- life extension technologies may demonstrate different chemical and pharmacological properties in participants than they do in laboratory studies. This technology and any programs resulting therefrom may not demonstrate the same chemical and pharmacological properties in humans and may interact with human biological systems in unforeseen, ineffective or harmful ways. In addition, we may in the future seek to discover and develop programs that are based on novel targets and technologies that are unproven. If our discovery activities fail to identify novel targets or technologies for drug discovery, or such targets prove to be unsuitable for treating human disease, we may not be able to develop viable additional programs. We and our existing or future collaborators may never receive approval to market and commercialize any product candidate. Even if we or an existing or future collaborator obtains regulatory approval, the approval may be for targets, disease indications or patient populations that are not as broad as we intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. If the products resulting from the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement prove to be ineffective, unsafe or commercially unviable, such programs would have little, if any, value, which would have a material and adverse effect on our business, financial condition, results of operations and prospects. Preclinical and clinical development involves a lengthy and expensive process that is subject to delays and with uncertain outcomes, and results of earlier studies and trials may not be predictive of future clinical trial results. If our preclinical studies and** clinical trials ~~and following~~ **are not sufficient to support** regulatory approval ~~. If we do not achieve one or more~~ of ~~these factors in a timely manner or at all, we could experience significant delays or an~~ **any of** ~~inability to successfully commercialize~~ our product candidates, **we** ~~which would materially harm our business. The results from our global pivotal PEACE Phase 3 trial~~ may **incur** ~~not support marketing approval, and the FDA or other regulatory authorities may require us to conduct~~ additional **costs** ~~non- clinical studies or clinical trials to evaluate subjects for~~ **or experience delays in completing,** ~~an additional follow- up period. We announced updated data from our~~ **or ultimately be unable** ~~ongoing PEACE Phase 3 trial in December 2021 and additional data in April 2022, and submitted a BLA~~ to **complete** ~~the FDA seeking full approval of pegzilarginase. On June 2~~ , ~~2022, we reported that we received a RTF Letter from~~ the **development** ~~FDA regarding the BLA. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. Even though the PEACE Phase 3 trial achieved statistical significance on its primary endpoint and a positive trend in a component~~ of **such** ~~the key secondary endpoint was observed, nominal statistical significance was not reached on any of the prespecified key secondary or secondary endpoints evaluating motor assessments. Even if we re- submit a BLA and the FDA files our BLA, the FDA may not conclude that the design of or results seen in the trial sufficiently demonstrate substantial evidence of effectiveness, including the demonstration of a clinically meaningful effect. The FDA also weighs the benefits of a~~ product ~~against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. We cannot predict whether any BLA we may submit in the future for pegzilarginase will be filed or approved in a timely manner or at all. We have initiated clinical trials with our product candidates -~~ **candidate** ~~, pegtarviliase and pegzilarginase. The risk of failure for all of our product candidates is high~~ . Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete ~~nonclinical development~~ **preclinical studies** and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product ~~candidates -~~ **candidate** in humans ~~for the respective target indications .~~ **Our** ~~Clinical~~ **clinical trials** ~~testing is expensive, difficult to design and implement, can take many -~~ **may** ~~years to~~ **not be conducted as planned or** ~~complete~~ **completed on schedule** , **if at all,** and ~~its outcome is inherently uncertain. Failure~~ **failure** can occur at any time during the **preclinical study or** clinical trial process. ~~The results~~ **For example, we depend on the availability** of ~~nonclinical~~ **NHPs to conduct certain preclinical** studies **that we are required to complete prior to submitting** ~~and -~~ **an** ~~early~~ **IND and initiating clinical development. There is currently a global shortage of NHPs available for drug development. This could cause the cost of obtaining NHPs for our future preclinical studies to increase significantly and, if the shortage continues, could also result in delays to our development timelines. Furthermore, a failure of one or more** clinical trials ~~of~~ **can** ~~our~~ **occur at any** ~~product candidates may not be predictive of the results of later-~~ stage **of testing. The outcome of** ~~clinical~~ **preclinical studies**

~~trials that will likely differ in design~~ and ~~size from~~ early- stage clinical trials ~~, and interim results~~ **may not be predictive** of **the success of later clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their product candidates. In addition, we expect to rely on participants to provide feedback on measures such as measures of quality of life, which are subjective and inherently difficult to evaluate. These measures can be influenced by factors outside of our control, and can vary widely from day to day for a particular participant, and from participant to participant and from site to site within** a clinical trial ~~do not necessarily predict final results~~ . **We cannot be sure that the FDA will agree** ~~For example, while we have observed a reduction in blood arginine and arginine metabolite levels due to administration of pegzilarginase in patients~~ with ~~Arginase 1 Deficiency, and a reduction in blood arginine levels due to pegzilarginase in patients with advanced solid tumors, these data may not necessarily be predictive of the final results of all patients treated with pegzilarginase, and may also not be predictive of pegzilarginase' s ability to reduce arginine or~~ **our** ~~arginine metabolite levels for these patients over a longer term nor predictive of positive~~ clinical ~~outcomes~~ **development plan** . **We plan** ~~In addition, while we intend~~ to ~~announce interim~~ **use the** data from our **planned Phase 1 trials of our SPY001 and SPY002 programs in healthy volunteers to support Phase 2 trials in IBD and other I & I indications. If the FDA requires us to conduct additional trials or enroll additional participants, our development timelines may be delayed. We cannot be sure that submission of an IND, BLA or similar application will result in the FDA or comparable foreign regulatory authorities, as applicable, allowing** clinical trials ~~from~~ **to begin in a** ~~time~~ **timely manner** ~~to time~~ , **if at all. Moreover, even if these trials begin, issues may arise that could cause regulatory authorities to suspend or terminate** such ~~reports~~ **clinical trials. Events that** may ~~be based~~ **prevent successful or timely initiation or completion of clinical trials include: inability to generate sufficient preclinical, toxicology or other in vivo or in vitro data to support the initiation or continuation of clinical trials; delays in reaching a consensus with regulatory authorities** on **study design** ~~unaudited data provided by our~~ **or implementation of the** clinical **trials; delays or failure in obtaining regulatory authorization to commence a** trial **; delays** ~~investigators. An audit or subsequent review of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we anticipate. In addition, our observations of clinical improvements, through clinician and assessor feedback or assessment tools~~ in **reaching agreement on acceptable terms** ~~the Phase 1 / 2 clinical trial, the Phase 2 open- label study, the PEACE Phase 3 clinical trial and its open- label extension of pegzilarginase in patients~~ with **prospective CROs** ~~Arginase 1 Deficiency after cumulative doses, may not be representative of our observations with subsequently dosed patients out to a similar or longer duration of cumulative dosing. We completed enrollment in our single, global pivotal PEACE Phase 3 clinical trial to evaluate the safety~~ and ~~efficacy of pegzilarginase in patients with Arginase 1 Deficiency. Due to COVID- 19, all of our~~ clinical trial sites ~~temporarily suspended screening~~ , **the terms of which can be subject** ~~limiting patient access, and resulting in some missed dosing appointments for patients. All patients that had initially paused dosing due~~ to **extensive negotiation and may vary significantly among different CROs and** ~~COVID- 19 had restarted treatment by September 2020. In addition, while we initiated dosing in our Phase 1 / 2~~ clinical trial **sites;** ~~investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, and began dosing in the third cohort in October 2022, the timing of continued enrollment may be delayed~~ **delays** in **identifying** ~~the future. Additionally~~ , **recruiting and training suitable** ~~missed doses by patients in our~~ clinical **investigators; delays** ~~studies may adversely affect the usefulness of the data collected~~ in ~~those~~ **obtaining required IRB approval at each clinical** ~~trials~~ **trial** ~~. It is impossible to predict when~~ **site; delays in manufacturing, testing, releasing, validating** or ~~if any~~ **importing / exporting sufficient stable quantities** of our product candidates ~~will prove effective or~~ **for** ~~safe~~ **use** in ~~humans or will receive regulatory approval. We may experience delays in our ongoing and planned~~ clinical trials ~~and we~~ **or the inability to** do **any of** ~~not know whether planned clinical trials will begin or enroll subjects on time, whether enrolled subjects will complete trials on time or at all, whether such trials will need to be redesigned or whether they~~ **the foregoing; failure by our CROs** ~~will be able to be completed on schedule~~ , ~~if at all. There can be no assurance that the~~ **other third parties or** ~~Health Authorities will allow~~ us to **adhere** ~~begin clinical trials or that they will not put any of the trials for any of our product candidates that enter or have entered clinical development on clinical hold in the future. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability~~ to ~~receive marketing approval or commercialize our product candidates. Clinical trials may be delayed, suspended or prematurely terminated because costs are greater than we anticipate or for a variety of reasons, such as: • delay or failure in reaching agreement with the Health Authorities on a trial design that we are able to execute; • delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical trial; • delays in reaching, or failure to reach, agreement on acceptable clinical trial contracts or~~ clinical trial protocols **; failure to perform in accordance** with ~~planned trial sites~~ **the FDA' s or any other regulatory authority' s good clinical practice requirements (" GCPs ") or applicable regulatory guidelines in other countries** ; **changes** ~~• modifications~~ to **the** ~~our ongoing and planned~~ clinical trial protocols ~~due to~~ **; clinical sites deviating from trial protocol or dropping out of a trial; changes in** regulatory requirements **and guidance that require amending** or ~~decisions made~~ **submitting new clinical protocols; selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data; transfer of manufacturing processes to facilities operated** by **a contract manufacturing organization (" CMO") and delays or failure by our CMOs 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. We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such clinical trials are being conducted, by the Data Safety Monitoring Board, if any, for such clinical trial or by the FDA or comparable foreign** regulatory authorities **. Such** ~~; • geographic complexities of managing the design and completion of clinical trials across different Health Authorities~~ **authorities** ~~in the United States, Canada, Europe, Australia, and other jurisdictions where we currently or may in the future~~

~~conduct clinical trials; • reports of safety issues, side effects or dose- limiting toxicities, or any additional or more severe safety issues in addition to those observed to date; • inability, delay or failure in identifying and maintaining a sufficient number of trial sites, many~~ **may suspend** ~~of which may already be engaged in other clinical programs; • delay or failure in recruiting and enrolling suitable subjects to participate in one or more clinical trials; • delay or failure in having subjects complete a trial or return for~~ **or terminate a** ~~post- treatment follow- up. For instance, one patient withdrew from the Phase 1 / 2~~ clinical trial **due** ~~of pegtarviliase for Classical Homocystinuria and two~~ **to** ~~patients previously dosed in our Phase 1 / 2~~ **a number of factors, including failure to conduct the** clinical ~~trial of pegzilarginase for the treatment of Arginase 1 Deficiency withdrew from the trial due to personal reasons; • clinical sites and investigators deviating from the trial protocol, failing to conduct the~~ trial in accordance with regulatory requirements or ~~dropping out of a trial; • a clinical hold for any of our ongoing or~~ **our** ~~planned clinical trials, including for pegtarviliase or pegzilarginase, where a clinical hold in a trial in one indication could result in a clinical hold for clinical trials in other indications; • failure of the Company, third party manufacturers, or sites participating in our clinical trials to pass regulatory inspections under applicable standards, including Good Clinical Practice and Good Manufacturing Practice; • clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct more clinical trials than we anticipate or abandon product development programs; • the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or insufficient or participants may drop out of these clinical trials at a higher rate than we anticipate; • we may experience delays or difficulties in the enrollment of patients, including the identification of patients with Classical Homocystinuria or Arginase 1 Deficiency; • our third- party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all; • we may have difficulty partnering with experienced CROs that can run our clinical trials effectively, adhere to the trial protocols and follow policies and procedures; • regulators may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks or privacy concerns; • the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; or • there may be changes in governmental regulations or administrative actions. If we are required to modify our ongoing~~ clinical trial 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 the programs, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we are required to** conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully ~~initiate or~~ complete clinical trials of our product candidates ~~or other testing~~, if the results of these trials **are not positive or are only moderately positive or if there are safety concerns,** ~~or~~ **our** ~~tests~~ **business and results of operations may be adversely affected and we may incur significant additional costs. We are researching the potential use of complementary diagnostics in connection with the development of our product candidates, and although we** do not ~~demonstrate sufficient clinical benefit~~ **currently anticipate such diagnostics would be required** ~~or for~~ ~~if~~ **the regulatory approval of any of** our product candidates **, they may be helpful to maximize the clinical and commercial success of our product candidates and if we fail to develop such complementary diagnostics or obtain regulatory approvals that may be required if they will be used commercially alongside any of our product candidates, our products may not be as competitive or commercially successful as they could be. A complementary diagnostic is a medical device, often an in vitro device, which provides information that is valuable for the safe and effective use of a corresponding therapeutic drug or biologic product. A complementary diagnostic can be used to identify patients or subsets of patients who are most likely to benefit from the therapeutic product. A complementary diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product. The development path of a complementary diagnostic may include additional meetings with regulatory authorities, such as a pre- submission meeting and the requirement to submit an investigational device exemption application. In the case of a complementary diagnostic that is designated as " significant risk device, " approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate. To be successful in developing, validating, obtaining approval of and commercializing a complementary diagnostic, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for complementary diagnostic tests on our own, we may require additional personnel. We may rely on third parties for the design, development, testing, validation and manufacture of complementary diagnostic tests for our therapeutic product candidates that may benefit from such tests, the application for and receipt of any required regulatory approvals, and the commercial supply of these complementary diagnostics. Although we currently plan to focus our complementary diagnostic development program on diagnostics that may help to identity high / better responding patients for our product candidates, we** do not ~~have~~ **believe such complementary diagnostics will be required by regulatory authorities in connection with granting regulatory approval for our product candidates but may aid in clinical trial recruitment, post-approval treatment decisions** ~~an~~ **and** ~~acceptable safety profile,~~ **maximizing the commercial success of our product candidates. If** we ~~may~~ **or third parties we engage are unable to successfully develop complementary diagnostics for our product candidates, or experience delays in doing so** : • **we may** be ~~delayed in obtaining marketing approval~~ **unable to maximize our potential to identify appropriate patients** for **enrollment in** our **clinical trials, which may adversely affect the development of our therapeutic** product candidates; • ~~not~~ **if the FDA or other regulators determine that the safe and effective use of our therapeutic product candidates, if any, depends on the complementary diagnostics we develop then we would have to expend time and resources to** obtain ~~marketing~~ **regulatory** approval ~~at all; •~~ **of such complementary**

diagnostics which could ~~cease~~ **cause** ~~development~~ **delays in the commercial launch or success** of our product candidates; **and** • **we may not realize the full commercial potential of any therapeutics that receive marketing approval. As a result of any of these events, our business, financial condition, results of operations and prospects could be materially and adversely affected. To be successful in developing and commercializing therapeutic product candidates in combination with diagnostic candidates, we will need to address a number of scientific, technical, regulatory and logistical challenges. We currently anticipate that we or a collaborator may need to obtain marketing authorization from the FDA in order to legally market such diagnostics in the United States. As a company, we have little experience in the development of diagnostic tests and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval, and have never applied for or obtained regulatory clearance or approval of any such diagnostic tests. Given our limited experience in developing diagnostic tests, we may rely in part or in whole on third parties for their design, development and manufacture of such tests. Before a new medical device, or a new intended use of, claim for, or significant modification to an existing device, can be marketed in the United States, a company must first submit an application for and receive 510 (k) clearance pursuant to a premarket notification submitted under Section 510 (k) of the Federal Food, Drug, and Cosmetic Act (" FDCA "), de- novo classification, or PMA approval from FDA, unless an exemption applies. The PMA approval pathway, which we expect to pursue for our complementary diagnostic product candidates, requires an applicant to demonstrate the safety and effectiveness of the product based, in part, on valid scientific evidence, including, but not limited to, technical, preclinical, and clinical data. The 510 (k) pathway requires a FDA finding that the test is substantially equivalent to a legally marketed predicate device. If no legally marketed predicate can be identified to enable use of the 510 (k) pathway, the device is automatically classified under the FDCA into Class III, which generally requires PMA approval. However, for low- to moderate- risk novel devices, FDA allows for the possibility of marketing authorization through the " de novo classification " process rather than requiring the device to be subject to PMA approval. Products that are approved through a PMA application generally need prior FDA approval before modifications can be made that affect safety or effectiveness, and certain modifications to a 510 (k)- cleared device may also require FDA premarket review before the modified product can be marketed. If we are unable to successfully develop, obtain regulatory clearance for and commercialize diagnostics to pair with our therapeutic product candidates, it could adversely impact our ability to develop and generate revenue from our product candidates. We may pursue development of combination products that require coordination within the FDA and comparable foreign regulatory authorities for review of its device and biologic components. Although the FDA and comparable foreign regulatory authorities have systems in place for the review and approval of combination products such as ours, we may experience delays in the development and commercialization of our product candidates due to regulatory timing constraints and uncertainties in the product development and approval process. Of note, prior clearance or approval of one component of a combination product does not increase the likelihood that FDA will approve a later product combining the previously cleared product or approved active ingredient with a novel active ingredient. If we encounter difficulties enrolling participants in our future clinical trials, our clinical development activities could be delayed or otherwise adversely affected. We may experience difficulties in patient participant enrollment in our future 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 participants who remain in the trial until its conclusion. The enrollment of participants in future trials for any of our programs will depend on many factors, including if participants choose to enroll in clinical trials, rather than using approved products, or if our competitors have ongoing clinical trials for programs that are under development for the same indications as our programs, and participants instead enroll in such clinical trials. Additionally, the number of participants required for clinical trials of our programs may be larger than we anticipate, especially if regulatory bodies require the completion of non- inferiority or superiority trials. Even if we are able to enroll a sufficient number of participants for our future clinical trials, we may have difficulty maintaining participants in our clinical trials. Our inability to enroll or maintain a sufficient number of participants would result in significant delays in completing clinical trials or receipt of marketing approvals and increased development costs or may require us to abandon one or more clinical trials altogether. Preliminary, " topline " or interim data from our clinical trials that we announce or publish from time to time may change as more participant data become available and are subject to audit and verification procedures. From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and 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. We also make assumptions, estimations, calculations and conclusions as part of our analyses of these data without the opportunity to fully and carefully evaluate complete data. As a result, the preliminary or topline 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 or subsequently made subject to audit and verification procedures. Any preliminary or topline 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 are subject to the risk that one or more of the clinical outcomes may materially change as participant enrollment continues and more participant data become available or as participants from our clinical trials continue other treatments. 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 product candidate, 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 preclinical study or clinical trial is based on what is typically extensive information, and you or**

others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the preliminary, topline or interim data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for **, and commercialize,** ~~indications or patient populations that are not as broad as intended or desired; • obtain approval with labeling that includes significant use or distribution restrictions or safety warnings that would reduce the potential market for~~ our product candidates ~~or inhibit our ability to successfully commercialize our product candidates; • be subject to additional post- marketing restrictions, requirements, and / or testing requirements; or • have the product removed from the market after obtaining marketing approval. We do not know whether any of our planned or current nonclinical studies, or ongoing or planned clinical trials, will need to be restructured or will be completed on schedule, or at all. For example, in June 2017, we delayed enrollment of pediatric patients in our Phase 1 / 2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency due to a difference in opinion with the FDA on data required to support inclusion of pediatric patients. Although we reached an agreement with the FDA in November 2017 and began dosing pediatric patients, the FDA~~ may ~~require additional information or studies to~~ be ~~conducted~~ **harmed** , **which** ~~or impose conditions that~~ could ~~further delay or restrict our other planned clinical activities in the future. Similarly, in October 2022, we received a letter from the FDA regarding a protocol amendment for our Phase 1 / 2 clinical rial of pegtarviliase in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less an 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. We began our global pivotal PEACE Phase 3 clinical trial in which we are studying plasma arginine reduction from baseline over 24 weeks as our primary endpoint. However, evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as our secondary endpoints, consisting of clinical outcome assessments focused primarily on mobility, as well as clinician and caregiver global impressions of effectiveness, may be required in addition to the primary endpoint to support approval. Certain of our clinical outcome secondary endpoints are being measured using motor assessments that have not been previously validated for Arginase 1 Deficiency, including the gross motor function classification system. Such motor assessments have only been validated in ambulatory children with cerebral palsy. We believe these motor functional assessments are translatable to Arginase 1 Deficiency patients given the similarities in symptoms of children with cerebral palsy and the Arginase 1 Deficiency populations, however the FDA or other Health Authorities may disagree. For example, on June 2, 2022, we reported that we received a RTF Letter from the FDA regarding our BLA submission for pegzilarginase. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. Significant nonclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may materially~~ harm our business ~~and~~ **, operating** results ~~of operations. The outbreak of the novel strain of coronavirus~~ , **prospects** ~~SARS- CoV- 2 and its variants, which causes COVID- 19, has, and may continue to, adversely impact our~~ **or** ~~business, including supply chain interruptions, and delays for raw materials. Public health crises such as pandemics or similar outbreaks could adversely impact our business. Timely enrollment in our clinical trials is dependent upon global clinical trial sites which may be adversely affected by global health matters, such as pandemics. We are currently conducting clinical trials for our product candidates in many countries, including the United States, Canada, Australia, United Kingdom and throughout the European Union. The regions in which we operate are currently being or may in the future be affected by COVID- 19. As a result of the COVID- 19 outbreak, or similar pandemics, we have experienced and may continue to experience disruptions that could severely impact our business, clinical trials and nonclinical studies, including: • delays or disruptions in nonclinical experiments and supplies for such experiments, including animals required for such experiments; • delays or disruptions in investigational new drug application- enabling good laboratory practice standard toxicology studies due to unforeseen circumstances in our supply chain; • increased rates of patients missing dosing appointments or withdrawing from our clinical trials following enrollment as a result of contracting COVID- 19, being forced to quarantine, and other travel restrictions, or not accepting home health visits and such missed doses by patients may adversely affect the usefulness of the data collected in our trials; • interruption of key clinical trial activities, such as clinical assessments at pre- specified timepoints during the trial and clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal, state, or foreign governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non- essential), which may impact the integrity of subject data and clinical study endpoints; • interruption of, or delays in receiving, supplies of our product candidates from our CMOs due to staffing shortages, production slowdowns or stoppages, disruptions in delivery systems; and • delays and interruptions to the supply chain, including the raw materials and other supplies needed for analysis and manufacturing of our product candidates. The trading prices for our common stock and other biopharmaceutical companies, as well as the broader equity and debt markets, have been highly volatile as a result of the COVID- 19 pandemic and the resulting impact on economic activity. The COVID- 19 pandemic has also contributed to other macroeconomic conditions, including rising interest rates, inflation and potential recessions. As a result, we may face difficulties raising capital when needed, and any sales may be on unfavorable terms to us. Further, to the extent we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of existing stockholders will be diluted. We may not be able to submit INDs, or foreign equivalents outside of the United States, to commence clinical trials for product candidates on the timeframes we expect, and even if we are able to, the Health Authorities may not permit us to proceed with planned clinical trials. Progression of any candidate into clinical trials is inherently risky and dependent on the results obtained in nonclinical programs, and other potential results such as the results of other clinical programs and results of third- party programs. If results are not available when expected or problems are identified during therapy development, we may experience significant delays in clinical development. This may also impact our~~

ability to achieve certain financial **condition** milestones and the expected timeframes to market any of our product candidates. **Our** Additionally, commencing any future clinical trials is subject to finalizing the trial design and submitting an IND, CTA or comparable submission in other jurisdictions. Even after we submit an IND, CTA or comparable submission in other jurisdictions, the Health Authorities could disagree that we have satisfied their requirements to commence our **or** clinical trials, disagree with our study design, or may change their guidance criteria, which may require us to complete additional nonclinical studies or amend our protocols or impose stricter conditions on the commencement of clinical trials. Failure to submit or have effective INDs, CTAs or other comparable foreign equivalents and commence clinical programs will ultimately limit our opportunity to generate revenue. Engineered human enzyme products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the trial period, the manufacturing and quality control standards required to be met by regulators, the number of patients the Health Authorities will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of engineered human enzyme products, or that the data generated in these **those of** trials will be acceptable to the FDA or **our future collaborators may reveal significant adverse events** another applicable regulatory authority to support marketing approval. In order to obtain marketing approval for **or** any of our product candidates, we must demonstrate the safety and efficacy of the product candidate for the relevant clinical indication or indications through nonclinical studies and clinical trials as well as additional supporting data. If our product candidates are associated with undesirable side effects **not seen** in nonclinical **our preclinical** studies **and may result in a safety profile that could halt clinical development, inhibit regulatory approval or limit commercial potential or market acceptance of any of** or **our product candidates. Results of our** clinical trials **could reveal a high and unacceptable severity and prevalence of**, in monotherapy or combination therapy, or have characteristics that are unexpected, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects **, adverse events** or other **unexpected** characteristics **. While** are less prevalent, less severe or **our preclinical studies in NHPs** more acceptable from a risk- benefit perspective. We are also conducting a Phase 1 / 2 trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. We have **not shown** also completed the global pivotal PEACE Phase 3 trial and a Phase 1 / 2 clinical trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency. Pegzilarginase is continuing to be evaluated in an **any such characteristics to date, we have not yet initiated any** open- label extension study for patients with Arginase 1 Deficiency that participated in our previous clinical trials. Given the nature of the patient populations enrolled in these trials, we have observed and expect to continue to observe serious adverse events that could be related or unrelated to pegzilarginase and could impact the safety or efficacy of pegzilarginase and we may observe serious adverse events that could be related or unrelated to pegtarviliase and could impact the safety or efficacy of pegtarviliase. We have also dosed, and may continue to dose, patients with pegzilarginase following compassionate use requests. While such patients are not monitored as part of our ongoing clinical trials, the occurrence of significant adverse events in such patients may negatively impact the prospects of our programs. In our prior clinical trials of pegzilarginase for the treatment of patients with advanced solid tumors and for the treatment of the patients with hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. We have reported results from these trials in which we observed serious adverse events that were considered possibly or probably related to the administration of pegzilarginase including asthenia, fatigue, failure to thrive, hypertension, diarrhea, nausea, vomiting, dehydration, dizziness, intracranial hemorrhage, and encephalopathy. In our completed combination trial of pegzilarginase and pembrolizumab in patients with previously- treated small cell lung cancer, safety observations were consistent with prior studies of pegzilarginase in patients with cancer. In a completed Phase 1 / 2 clinical trial and the PEACE Phase 3 clinical trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency, we have observed serious adverse events in some patients, including hyperammonemia, hypersensitivity, and vomiting, which were infrequent, expected and manageable. Hyperammonemia is an important metabolic effect experienced by some patients with Arginase 1 Deficiency. None of the patients in these trials discontinued due to adverse events, while three patients discontinued for non- medical reasons. Subjects in our ongoing and planned clinical trials with pegtarviliase and pegzilarginase may suffer minor, significant, serious, or even life- threatening adverse events, including those that are drug- related. Subjects in our ongoing and planned clinical trials may also suffer side effects not yet observed in any of our prior and ongoing clinical or nonclinical studies, including, but not limited to, toxicities to the nervous system, liver, heart, lung, kidney, blood, pulmonary or immune system. We have not dosed any of our other product candidates in humans. **If** Certain COVID- 19 vaccines include pegylated components, which could result in the development of anti- PEG antibodies in vaccinated patients. Whether such antibodies have been developed, and their potential impact on the efficacy and safety of our product candidates is highly uncertain and cannot be predicted. Testing in animals, such as our primate studies for pegtarviliase and pegzilarginase may not uncover all side effects in humans or any observed side effects in animals may be more severe in humans. For example, it is possible that patients' immune systems may recognize our engineered human enzymes as foreign and trigger an immune response, including the production of anti- drug antibodies that could limit the activity of our human enzymes. We believe this risk may be heightened in patients with deficiencies in the enzyme activity our potential therapies are intended to correct, including patients with Arginase 1 Deficiency that we are treating with pegzilarginase in our open- label extension study, and any future clinical trials we conduct for this rare genetic disease. The risk of a patient developing an immune response, including anti- drug antibodies to our engineered enzymes, and the potential impact of the immune response on the efficacy and safety of our product candidates, cannot be predicted. In addition, our product candidates such as pegtarviliase and pegzilarginase break down target amino acids, thereby releasing metabolites into the bloodstream. Some patients may be sensitive to these metabolites, increasing the risk of an adverse reaction due to treatment, which risk may not be able to be mitigated through dosing. Finally, although our engineered human enzyme product candidates such as pegtarviliase and pegzilarginase are engineered from the human genome, pegtarviliase and pegzilarginase are produced in E. coli. This manufacturing process could lead to the products being more

~~likely to trigger an immune response than we expect. To the extent~~ significant adverse events or other side effects are observed in any of our **future** clinical trials, we may have difficulty recruiting ~~patients~~ **participants** to **such** ~~the clinical trial~~ **trials**, ~~patients~~ **participants** may drop out of our ~~trial~~ **trials**, or we may be required to abandon the ~~trial~~ **trials** or our development efforts of **one or more programs altogether. We, the FDA or other applicable regulatory authorities, or an IRB, may suspend any clinical trials of any program at any time for various reasons, including a belief** that ~~product candidate altogether~~ **subjects or patients in such trials are being exposed to unacceptable health risks or adverse side effects**. Some potential ~~therapeutics~~ **products** developed in the biotechnology industry that initially showed therapeutic promise in early- stage studies **and trials** have later been found to cause side effects that prevented their further development. **Other potential products have shown side effects in preclinical studies, which side effects do not present themselves in clinical trials in humans.** Even if the side effects do not preclude the ~~drug~~ **product candidate** from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. **In addition, an extended half- life could prolong the duration of undesirable side effects, which could also inhibit market acceptance. Treatment- emergent adverse events could also affect participant recruitment or the ability of enrolled subjects to complete our clinical trials or could result in potential product liability claims. Potential side effects associated with our product candidates may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from our product candidates may not be normally encountered in the general patient population and by medical personnel.** Any of these ~~developments~~ **occurrences** could ~~materially~~ harm our business, financial condition **, results of operations** and prospects **significantly**. ~~Further~~ **In addition**, ~~toxicities associated with~~ **even if we successfully advance** our product candidates **or any future** ~~may also develop after regulatory approval and lead to the withdrawal of the~~ product ~~from the market~~ **candidates through clinical trials, such trials will only include a limited number of participants and limited duration of exposure to our product candidates**. ~~We~~ **As a result, we** cannot ~~predict whether~~ **be assured that adverse effects of** our product candidates will ~~cause organ or~~ **not be uncovered when a significantly larger number of participants are exposed to** ~~other~~ -- **the product candidate after** ~~injury in humans that would preclude or lead to the revocation of regulatory~~ approval ~~based on nonclinical studies or early stage clinical testing~~. **Further, any** ~~Delays or difficulties in the enrollment of patients in our ongoing or planned~~ clinical trials ~~, could delay or prevent our receipt of necessary regulatory approvals. We~~ may not be ~~able to initiate or continue our ongoing or planned clinical trials if we are unable to locate and enroll a~~ sufficient ~~number of eligible patients to participate in these trials as required by the Health Authorities. For example, we are currently enrolling in our Phase 1 / 2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria, the timing of which has been impacted by COVID- 19. While we initiated dosing in our Phase 1 / 2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, and reported in November 2022 that dosing of two~~ -- **to determine** ~~patients in the third cohort was complete, the timing of continued enrollment may be delayed in the future. Further, we previously submitted a protocol amendment for our Phase 1 / 2 clinical trial of pegtarviliase, which, among other~~ -- **the effect** ~~things, requested the inclusion of adolescent patients at clinical trial sites in the United States. The FDA stated the protocol did not provide adequate justification~~ and **safety consequences** ~~evidence to support the prospect~~ of **using** ~~direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age under this IND at this time. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. Furthermore, many of~~ our product candidates ~~, including pegtarviliase and pegzilarginase, initially target indications that may be characterized as orphan markets,~~ **over a multi- year period. If any of the foregoing events occur or if one or more of the research programs with respect to** which **we have exercised** ~~can prolong the clinical trial timeline if sufficient patients cannot be enrolled in a timely manner. Arginase 1 Deficiency is a rare disorder, and there~~ -- **the Option to acquire intellectual property license rights to or have** ~~are no published reports of disease prevalence. Based on an internal analysis of published literature and other~~ -- **the Option** ~~data sources, we estimate the prevalence of Classical Homocystinuria~~ to **acquire intellectual property license rights to pursuant to** ~~be approximately 30, 000 in global addressable markets, with 80 % of those~~ -- **the Paragon Agreement prove** ~~patients being potential treatment candidates due~~ to ~~their inability to control tHey levels with currently available treatments. Of the approximately 25, 000 treatment candidates in global addressable markets, including B6- non- responsive and B6- partially- responsive patients, approximately 8, 500 are estimated in the key commercial markets of the United States, France, Germany, Italy, Spain, and the United Kingdom. However, we may not~~ be **unsafe,** ~~able to continue to enroll the trial as expected or~~ **our entire pipeline** ~~locate and enroll a sufficient number of eligible patients as required by the Health Authorities, and the necessary regulatory approvals~~ could be ~~delayed or prevented. We commissioned a genetic prevalence analysis and based on that analysis estimate the Arginase 1 Deficiency population is greater than 2, 500 patients in the global addressable markets and greater than 1, 150 patients in the territories with regulatory and launch plans underway. The genetic prevalence- based methodology is intended to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U. S. states (plus the District of Columbia) perform newborn screening for Arginase 1 Deficiency, and newborn screening is not currently widely performed in European countries. Delays in patient enrollment could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether. Patient enrollment is~~ affected ~~by factors including: • the severity of the disease under investigation; • the design of the clinical trial protocol; • the novelty of the product candidate and acceptance by physicians; • the patient eligibility criteria for the study in question; • the size of the total patient population; • the design of the clinical trials; • the perceived risks and benefits of the product candidate under study; • our commercialization strategy; • the availability and efficacy of competing therapies and clinical trials; • our payments for conducting clinical trials; • the patient referral practices of physicians; • the ability to monitor patients adequately during and after treatment with the product candidate; • the proximity and availability of~~

clinical trial sites for prospective patients; and • the impact of COVID- 19 or another epidemic or pandemic and related local restrictions. The safety or efficacy profile of our current or future product candidates may differ in combination therapy with other existing or future drugs, and therefore may preclude its further development or approval . which would **have a** materially - - **material** harm **adverse effect on** our business . From time to time , **financial condition, results** our commercialization strategy may include the combination of **operations and prospects. We may expend** our product candidates with third- party products or **our limited resources** product candidates. For example, we completed a combination trial with Merck to **pursue a particular program and fail** evaluate the combination of pegzilarginase with Merck' s anti- PD- 1 therapy, KEYTRUDA ® (pembrolizumab), for the treatment of patients with small cell lung cancer. Such combination studies involve additional risks due to **capitalize** their reliance on **programs** circumstances outside our control, such as those relating to the availability and marketability of the third- party product involved in the study. Additionally, we may be unable to secure and maintain a sufficient supply of such third- party products when needed on commercially reasonably terms. Any such shortages could cause us to delay or terminate our combination trials. It is also difficult to predict the way in which pegzilarginase, or any current or future product candidate, will interact with third- party products used in combination clinical trials. As a result, such combination trials may demonstrate reduced efficacy, increase or exacerbate side effects that have been seen with pegzilarginase, or any current or future product candidate, alone, or result in new side effects that have not previously been identified with pegzilarginase, or any current or future product candidate, alone. In addition, data obtained from any combination trials may be **more profitable** subject to a variety of interpretations. For - **or** instance, positive data may not guarantee the ability to move forward due to changes in the competitive or regulatory environment for the treatment of targeted indications, and failure to achieve our primary endpoints may not necessarily preclude a viable commercial path. Any undesirable side effects, lack of efficacy seen in combination trials, changing regulatory and commercial requirements for approval, differing interpretation of clinical data or other unforeseen circumstances may affect our ability to continue with and obtain regulatory approval for the combination therapy, as well as our ability to continue with and obtain regulatory approval for pegzilarginase monotherapy. Further, evaluating pegzilarginase, or any current or future product candidate, in combination with other products in clinical development may require us to establish collaborations, licensing arrangements or alliances with third parties. There is no assurance that we will be able to enter into such arrangements on favorable terms, or at all. Even though we have obtained orphan drug designation for pegtarviliase in the United States and Europe for the treatment of patients with Homocystinuria and for pegzilarginase in the United States and Europe for the treatment of Arginase 1 Deficiency (hyperargininemia), we may not obtain or maintain orphan drug exclusivity for pegtarviliase or pegzilarginase and we may not obtain orphan drug designation or exclusivity for any of our other product candidates or indications. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs or biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200, 000 individuals in the United States. Similarly, the European Commission may designate a product as an orphan drug under certain circumstances. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same disease during that time period. The applicable period is seven years in the United States and ten years in the European Union. The European Union exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. We have received orphan drug designation in the United States and Europe for pegtarviliase for the treatment of patients with Homocystinuria. We have also received orphan drug designation in the United States and Europe for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. This orphan drug exclusivity prevents the FDA or the EMA from approving another application, including a BLA in the United States or a MAA in the European Union, to market a drug containing the same principal molecular structural features for the same orphan indication, except in very limited circumstances, including when the FDA or the EMA concludes that the later drug is safer, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Even though we have received orphan drug designation for pegtarviliase for the treatment of patients with Homocystinuria in the United States and Europe and for pegzilarginase for the treatment of Arginase 1 Deficiency in the United States and Europe, we may not be the first to obtain marketing approval for the orphan- designated indication in these jurisdictions due to the uncertainties associated with developing pharmaceutical product candidates. We may also seek to obtain orphan drug designations in other international jurisdictions. However, there is no guarantee that we would be able to do so on a **greater** timely basis, or at all. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or a drug with the same principal molecular structural features can be approved for a different indication. Orphan drug designation by the FDA or the EMA 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. In addition, even if we intend to seek orphan drug designation for other product candidates or indications, we may never receive such designations or obtain orphan drug exclusivity. A Rare Pediatric Disease designation by the FDA does not guarantee that the NDA or BLA for the product will qualify for a priority review voucher upon approval, and it does not necessarily lead to a faster development or regulatory review process, or increase the likelihood that any of our product candidates will receive marketing approval. Under the Rare Pediatric Disease Priority Review Voucher Program, upon the approval of a qualifying BLA or NDA for the treatment of a rare pediatric disease, the sponsor of such an

application would be awarded a transferable rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent BLA or NDA. In September 2018, the FDA notified us that we obtained Rare Pediatric Disease designation for pegzilarginase for the treatment of patients with Arginase 1 Deficiency, and in November 2020, the FDA notified us that we obtained Rare Pediatric Disease designation for pegtarviliase for the treatment of Homocystinuria. On December 27, 2020, the Creating Hope Reauthorization Act extended the Rare Pediatric Disease Priority Review Voucher Program, and after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers. However, there is no guarantee that any of our product candidates will be approved by that date, or at all, and, therefore, we may not be in a position to obtain a priority review voucher prior to expiration of the program, unless Congress further reauthorizes the program. Additionally, designation of a drug for a rare pediatric disease does not guarantee that a BLA will meet the other eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Finally, a Rare Pediatric Disease designation does not necessarily lead to faster development or regulatory review of the product, or increase the likelihood that it will receive marketing approval. Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad. In order to market and sell our products in the European Union and many other jurisdictions, we or our third- party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing and different criteria for approval. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We, or our third- party collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, failure to obtain approval in some countries or jurisdictions may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. We or third parties may not be successful --- **success** in developing diagnostic assays, or enhanced biomarker approaches, if required for our product candidates. In developing a product candidate for some indications, we may decide to use a biomarker- based test to identify patients for enrollment and, or, monitor patients in clinical trials or in the commercial environment, which could require development of new and / or modification of existing biochemical monitoring approaches. In such case, the FDA may require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. Alternatively, there may be clinical benefits for some enzyme- based therapies in enhancing currently available biochemical monitoring approaches. While we are not aware of any precedents requiring such approaches for regulatory approval, the FDA or other regulatory authorities could request that new biochemical monitoring approaches are available to support some product candidates. Clinical trials that utilize a biomarker- based test to select patients are likely to take longer and require additional funding. We do not have experience or capabilities in developing or commercializing these companion diagnostics and plan to rely in large part on third parties to perform these functions. Some diagnostic assays are subject to regulation by the FDA as medical devices and require separate regulatory approval prior to the use of such diagnostic assays with a therapeutic product candidate. If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostic assays for use with our product candidates, or experience delays in development, we may be unable to identify patients with the specific profile targeted by our product candidates for enrollment in our clinical trials. Accordingly, further investment may be required to further develop or obtain the required regulatory approval for the relevant diagnostic assay, which would delay or substantially impact our ability to conduct further clinical trials or obtain regulatory approval. In addition, if a companion diagnostic is necessary for any of our product candidates, a delay in the development of the assay, or the delay or failure to obtain regulatory approval of the companion diagnostic would delay or prevent the approval of the therapeutic product candidate. Alternatively, we may also make the decision that our therapy does not require a companion diagnostic, however the Health Authorities may disagree and require the development and regulatory approval of a companion diagnostic assay as a condition of approval of the product candidate, creating additional costs and a delay in bringing our product candidate to market. We may in the future expand our development and regulatory capabilities and potentially implement commercialization capabilities, and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. If we seek to expand our development and regulatory capabilities in the future, we will need to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of product candidate development and regulatory affairs. Further, if any of our product candidates receives marketing approval, we would need to expand operations with respect to sales, marketing, access, reimbursement, and distribution. We currently do not have a fully integrated commercial team to distribute and market our product candidates following regulatory approval, if approved. In order to commercialize any product candidates, we must build on a territory- by- territory basis marketing, sales, distribution, managerial and other non- technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If our product candidates receive regulatory approval, we intend to establish a fully integrated commercial organization with technical expertise and supporting distribution capabilities to commercialize our product candidates in certain markets, which will be expensive and time consuming and will require significant attention of our executive officers to manage. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel in such markets. Any failure or delay in the development of our internal sales, marketing, access, reimbursement, and distribution capabilities would adversely impact the commercialization of any of our

product candidates that we obtain approval to market. With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory- by- territory basis, 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. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. For example, in March 2021, we entered into a licensing agreement with Immedica, in which Immedica acquired the product rights for commercialization of pegzilarginase in the European Economic Area and certain Middle East jurisdictions. We may have little or no control over the marketing and sales efforts of such third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses. To manage any future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a public company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations. We may not be successful in our efforts to identify additional product candidates. Due to our limited resources and access to capital, we must prioritize development of certain product candidates, which may prove to be wrong and may adversely affect our business. Although we intend to explore other therapeutic opportunities, in addition to the product candidates that we are currently developing, we may fail to identify viable new product candidates for clinical development for a number of reasons. If we fail to identify additional potential product candidates, our business could be materially harmed. Research programs to pursue the development of our existing and planned product candidates for additional indications and to identify new product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. Our research programs may initially show promise in identifying potential indications and / or product candidates, yet fail to yield results for clinical development for a number of reasons, including: • the research methodology used may not be successful in identifying potential indications and / or product candidates; • potential product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs; • it may take greater human and financial resources than we will possess to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our product portfolio; or • alternative research or therapeutic methodologies may be more efficient than the research approaches we have provided . Because we have limited financial and human **managerial** resources, we intend to **focus our research and development efforts on certain selected programs. For example, we are** initially focus **focused** on research **our most advanced** programs **, SPY001** and **SPY002** product candidates for a limited set of indications . As a result, we may forego **forgo** or delay pursuit of opportunities with other **programs** product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success . Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. **Our spending on current and future research and development programs** Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our **specific indications may not yield any commercially viable** product candidates or to develop suitable **. If we do not accurately evaluate the commercial** potential product candidates through internal research programs, which could materially adversely affect our **or target** future growth and prospects. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful. Risks Related to Commercialization If the market opportunities for our product candidates are smaller than we believe they are, our future product revenues may be adversely affected, and our business may suffer. Our understanding of both the number of people who suffer from conditions such as Classical Homocystinuria and Arginase 1 Deficiency, as well as the potential subset of those who have the potential to benefit from treatment with our product candidates, are based on estimates. We expect our product candidates targeting rare diseases to target a **particular** smaller subset of patient populations that suffer from the respective diseases we seek to treat. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, Europe or elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our product candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects. Further, there are several factors that could contribute to making the actual number of patients who receive our potential product candidates less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Additionally, our assumptions regarding the addressable market may be incorrect and the addressable market may change over time, including from the announcement date of a product candidate **, we may relinquish valuable rights** to **that product candidate through collaboration, licensing or** the **other** approval by Health Authorities **royalty arrangements in cases in which it would have been more advantageous for us to retain sole development** and commercialization **rights to such** . Even if we obtain significant market share for our product candidates **candidate** , because certain of the potential target populations are small, we **. Any approved products resulting from our current programs or any future program** may never **not** achieve **adequate** profitability without obtaining regulatory approval for additional

~~indications. Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of~~ market acceptance ~~by physicians~~ **among clinicians** , patients, **healthcare** third- party payors and others in the medical community necessary for commercial success **and we may not generate any future revenue from the sale or licensing of such products** . Even if ~~any~~ **regulatory approval is obtained for a product candidate resulting from one** of **our current** ~~our~~ **or future programs, they may not gain market acceptance among physicians, patients, healthcare payors or the medical community. We may not generate or sustain revenue from sales of the product due to factors such as whether the product can be sold at a competitive cost and whether it will otherwise be accepted in the market. There are several approved products and** product candidates ~~receives marketing~~ **in later stages of development for the treatment of IBD. However, our programs incorporate advanced antibody engineering to optimize the half- life and formulation of antibodies; to date, no such antibody has been** ~~approval~~ **approved** ~~, it may nonetheless fail to gain sufficient~~ **by the FDA for the treatment of IBD.** ~~market~~ **Market participants with significant influence over** acceptance ~~by physicians~~ **of new treatments** , ~~patients,~~ **such as clinicians and** third- party payors **, may not adopt a biologic that incorporates half- life extension for our targeted indications,** and ~~others in~~ **we may not be able to convince** the medical community ~~necessary~~ **and third- party payors to accept and use, or to provide favorable reimbursement** for ~~commercial success~~ **, any programs developed by us or our existing or future collaborators** . ~~Current~~ **An extended half- life may make it more difficult for patients to change** treatments ~~for Homocystinuria include CYSTADANE ® (betaine anhydrous for oral solution)~~ and **there is a perception that half** ~~dietary restrictions. Current treatments for Arginase 1 Deficiency included dietary restrictions and, in some instances, ammonia~~ ~~scavenging drugs such as RAVICTI ® (glycerol phenylbutyrate)~~ **life extension could exacerbate side effects, each of which may adversely affect our ability to gain market acceptance** . ~~If~~ **Market acceptance of** our product candidates ~~do~~ **will depend on many factors, including factors that are not within our control. Sales of medical products also depend on the willingness of clinicians to prescribe the treatment. We cannot predict whether clinicians, clinicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our product is safe, therapeutically effective, cost effective or less burdensome as compared with competing treatments. If any current or future product candidate is approved but does** not achieve an adequate level of acceptance **by such parties** , we may ~~never~~ **not** generate ~~significant~~ **or derive sufficient revenue from that** product ~~revenues~~ **candidate** and ~~we~~ may not become **or remain** profitable. **Certain** ~~The degree~~ of ~~market acceptance of~~ our **programs may compete with our other programs, which could negatively impact our business and reduce our future revenue. We are developing** product candidates **for the same indication: IBD** , **and may in the future develop our programs for other I & I indications. Each such program targets a different mechanism of action. However, developing multiple programs for a single indication may negatively impact our business** if **the programs compete with each other. For example, if multiple programs are conducting clinical trials at the same time, they could compete for the enrollment of participants. In addition, if multiple product candidates are** approved for ~~commercial~~ **the** ~~sale~~ **same indication** , **they may compete for market share, which could limit our future revenue. We plan to conduct clinical trials for programs at sites outside the United States, and the FDA may not accept data from trials conducted in such locations. We may choose to conduct one or more of our future clinical trials outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U. S. population, and the data must be applicable to the U. S. population and U. S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data** will depend on **its determination that the trials also complied with all applicable U. S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time- consuming and would delay or permanently halt our development of the applicable product candidates. Even if the FDA accepted such data, it could require us to modify our planned clinical trials to receive clearance to initiate such trials in the United States or to continue such trials once initiated. Further, conducting international clinical trials presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled participants in foreign countries to adhere to clinical protocol as** a ~~number~~ **result of differences in healthcare services or cultural customs that could restrict or limit our ability to conduct our clinical trials, the administrative burdens of conducting clinical trials under multiple sets of foreign regulations, foreign exchange fluctuations, diminished protection of intellectual property in some countries, as well as political and economic risks relevant to foreign countries. The regulatory approval processes of the FDA and other comparable foreign regulatory authorities are lengthy, time- consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our product candidates, we will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired. The process of obtaining regulatory approvals, both in the United States and abroad, is unpredictable, expensive and typically takes many years following commencement of clinical trials, if approval is obtained at all, and can vary substantially based upon a variety** of factors **, including the type, complexity and novelty of the product candidates involved. We cannot commercialize product candidates in the United States without first obtaining regulatory approval from the FDA. Similarly, we cannot commercialize product candidates outside of the United States without obtaining regulatory approval from comparable foreign regulatory authorities. Before obtaining regulatory approvals for the commercial sale of our product candidates, including our most advanced product candidates, SPY001 and SPY002, we must demonstrate through lengthy, complex and expensive preclinical studies and clinical trials that our product candidates are both safe and effective for each targeted indication. Securing regulatory approval also requires the submission of information about the drug manufacturing process to, and**

inspection of manufacturing facilities by, the relevant regulatory authority. Further, our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval. The FDA and comparable foreign regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other data. Our product candidates could be delayed in receiving, or fail to receive, regulatory approval for many reasons , including: ~~• the FDA application.Approval of our product candidates may be delayed~~ or **comparable foreign regulatory** ~~refused for many reasons,including the following:• the Health Authorities~~ **authorities** may disagree with the design or implementation of our clinical trials; ~~•~~ we may be unable to demonstrate to the satisfaction of the ~~Health~~ **FDA or comparable foreign regulatory** ~~Authorities~~ **authorities** that ~~our~~ **a** product ~~candidates~~ - **candidate** ~~are~~ **is** safe and effective for **its** ~~any of their~~ proposed ~~indications~~ - **indication** ; ~~•~~ the results of clinical trials may not meet the level of statistical significance required by the ~~Health~~ **FDA or comparable foreign regulatory** ~~Authorities~~ **authorities** for approval; ~~•~~ **serious and unexpected drug- related side effects may be experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;** we may be unable to demonstrate that ~~our~~ **a** product ~~candidates~~ - **candidate** ' **s** clinical and ~~other benefits outweigh their safety risks;• the Health Authorities may disagree with our their~~ - **other** ~~efficacy,~~ **benefits outweigh its** safety ~~and~~ **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 acceptable or sufficient to support the submission of a BLA or** other **submission or** ~~potential advantages compared~~ to ~~alternative treatments~~ **obtain regulatory approval in the United States or elsewhere, and we may be required to conduct additional clinical trials** ; ~~• our ability to offer them~~ - **the FDA** ~~for~~ - **or** ~~sale at competitive prices~~ **the applicable foreign regulatory authority may disagree regarding the formulation, labeling and / or the specifications of our product candidates** ; ~~• their~~ -- **the FDA or** ~~convenience and ease of administration compared~~ - **comparable foreign regulatory authorities may fail** to **approve** ~~alternative treatments; • the willingness of the target patient population to try new therapies and of physicians to prescribe these~~ -- **the manufacturing processes or facilities** ~~therapies; • the ability of healthcare professionals to accurately identify and diagnose patients with the relevant / indicated condition; • the strength of marketing and distribution support; • the availability~~ of third- party ~~payor coverage and adequate reimbursement~~ **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. Of the large number of drugs in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market** our product candidates ~~; • the prevalence and severity~~ **, which would significantly harm our business, results** of ~~their side effects; •~~ **operations and prospects. If we were to obtain approval, regulatory authorities may approve** any ~~restrictions on the use~~ of our product candidates ~~together with other~~ **for fewer or more limited** ~~medications~~ **indications than** ~~; • interactions of our product candidates with other products patients are taking; and • inability of patients with certain medical histories to take our product candidates. We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if~~ we **request** ~~fail to compete effectively. The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and internationally~~ , including **failing to approve** ~~major multinational pharmaceutical companies, biotechnology companies, universities and other~~ -- **the most commercially promising indications** ~~research institutions. Many of our competitors have substantially greater financial~~ , ~~technical and~~ **may grant approval contingent on** ~~other~~ -- **the performance of costly post-** ~~resources, such as larger research and development staff and experienced~~ marketing **clinical trials,** ~~and manufacturing organizations and well- established sales forces. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for~~ - **or** ~~investment in these industries. Our competitors~~ may **approve a** ~~succeed in developing, acquiring or licensing, on an exclusive basis, product candidates that are more effective or less costly than any~~ product candidate **with a label** that ~~we are currently developing~~ **does not include the labeling claims necessary or desirable** ~~or~~ **for the successful commercialization of** that ~~we may develop. We anticipate a competitive landscape in Homocystinuria. There is currently one FDA- approved therapy for the treatment of Homocystinuria and multiple medical foods. CYSTADANE ® (betaine anhydrous for oral solution) was approved by the FDA in 1996 and is currently marketed in North America by Recordati Rare Diseases Inc. We are also aware of two investigational therapies in clinical development for the treatment of Homocystinuria. Travere Therapeutics Inc. is focused on the development of pegtibatinase, an enzyme replacement therapy in patients with Homocystinuria due to cystathionine β- synthase deficiency. Travere released topline data in December 2021 from its Phase 1 / 2 study of pegtibatinase which showed a 55 % reduction in homocysteine at the highest dose cohort (1. 5mg / kg, 2x / week). In January 2023, Travere stated that enrollment had been completed in the final cohort of their ongoing Phase 1 / 2 study and that the company is preparing for the initiation of a pivotal Phase 3 trial in the second half of 2023. SYNB1353 from Synlogic Inc. is also in clinical development for the potential treatment of Homocystinuria. In January 2023, the company announced completion of a Phase 1 study with anticipated advancement into Phase 2 in 2023. This investigational agent is an oral synthetic biotic platform that consumes methionine, an essential amino acid and precursor of homocysteine, in the gastrointestinal tract. We are also aware of two investigational therapies in preclinical development. The first is CDX- 6512, an oral methionine- gamma- lyase enzyme therapy from Codexis. Additionally, Erytech Pharma SA also has a~~ product candidate ~~for Homocystinuria in preclinical development~~ . **If we** ~~It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria. There~~ are ~~multiple approved treatments and investigational therapies for the management of hyperammonemia commonly experienced by patients with urea cycle disorders. While these products — known as ammonia scavengers — do~~ not

able to obtain ~~target the core metabolic defect of Arginase 1 Deficiency~~ , **or if** ~~they can help patients manage their~~ **there** ~~elevated ammonia levels. There~~ are **delays** ~~multiple marketed therapies to treat hyperammonemia associated with urea cycle disorders. Those include RAVICTI ® (glycerol phenylbutyrate) and BUPHENYL ® (sodium phenylbutyrate) from Horizon Therapeutics plc and OLPRUVATM (sodium phenylbutyrate) from Acer Therapeutics Inc.; additionally, at least one generic formulation of sodium phenylbutyrate is commercially available. We are aware of one other company with an investigational therapy for Arginase 1 Deficiency~~ in ~~preclinical stages, Erytech Pharma SA, who in February 2022 announced the allowance of a U. S. patent application covering arginine deiminase encapsulated into red blood cells for the treatment of Arginase 1 Deficiency. Our ability to compete successfully will depend largely on our ability to leverage our experience in product candidate discovery and development to: • discover and develop product candidates that are sufficiently differentiated from other products in the market; • attract qualified management, scientific, product development and commercial personnel; • obtain~~ **obtaining ,** ~~and maintain patent and / or other proprietary protection for our product candidates and technologies; • obtain~~ required regulatory approvals ~~; • successfully launch and commercialize our approved products; and • successfully collaborate with research institutions or~~ **for our** ~~pharmaceutical companies in the discovery, development and commercialization of new~~ product candidates ~~. The availability and price of~~ **, we will not be able to commercialize,** ~~our~~ **or** ~~competitors'~~ **will be delayed in commercializing, our product candidates and our ability to generate revenue will be materially impaired. We may not be able to meet requirements for the chemistry, manufacturing and control of our programs. In order to receive approval of our** products **by** ~~could limit~~ the **FDA** ~~demand,~~ and ~~the price~~ **comparable foreign regulatory authorities,** we **must show that we and our contract manufacturing partners** are able to ~~charge~~ **characterize** , ~~for~~ **control and manufacture our drug products safely and in accordance with regulatory requirements. This includes manufacturing the active ingredient, developing** ~~any~~ **an** ~~of our~~ **acceptable formulation, manufacturing the drug** product ~~candidates~~ , ~~if approved~~ **performing tests to adequately characterize the formulated product, documenting a repeatable manufacturing process, and demonstrating that our drug products meet stability requirements** . ~~We will~~ **Meeting these chemistry, manufacturing and control requirements is a complex task that requires specialized expertise. If we are** not **able** ~~achieve our business plan if acceptance is inhibited by price competition or the reluctance of patients, physicians, or third- party payors~~ to **meet the chemistry** ~~accept our product candidates. Established biotechnology companies may invest heavily to accelerate discovery and development of products that could make our product candidates less competitive. In addition~~ , **manufacturing** ~~any new product that competes with an~~ **and control requirements** ~~approved product must demonstrate compelling advantages in efficacy~~ , ~~convenience, tolerability and / or safety to establish a meaningfully differentiated value proposition for patients, physicians, and third- party payors. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA or non- U. S. regulatory approval or discovering, developing and commercializing product candidates before~~ we **may** ~~do, which would have a material adverse impact on our business. Many of our competitors have greater resources than we do and have established sales, marketing, and market access capabilities, whether internally or through third parties. We will~~ not be ~~able to successfully~~ -- **successful** ~~commercialize our product candidates without establishing sales and marketing capabilities internally or through strategic partners. The insurance coverage and reimbursement status of newly- approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current product candidates could limit our ability to market those product candidates and decrease our ability to generate revenue. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend substantially, both~~ in **getting** ~~the United States and internationally, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third- party payors. If 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. There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U. S. Department of Health and Human Services since CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours~~ - **our** ~~since there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries. Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost- containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the United Kingdom and the countries of the European Union, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost- effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits. Moreover, increasing efforts by~~

~~governmental and third- party payors, in the United States and internationally, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new~~ products approved ~~and, as a result, they may not cover or provide adequate payment for our product candidates. The U. S. government has similarly expressed concerns over the pricing of pharmaceutical products and there can be no assurance as to how this scrutiny will impact future pricing of pharmaceutical products generally. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market. In addition to CMS and private payors, professional organizations can influence decisions about reimbursement for new products by determining standards for care. In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our product candidates. Furthermore, some of our target indications, including Homocystinuria for pegtarviliase and Arginase 1 Deficiency for pegzilarginase, are orphan indications where patient populations are small. In order for therapeutics that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such therapeutics must be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product candidate that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for any future product candidates from third- party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect our ability to market or sell those product candidates, if approved, and ultimately our financial results .** Our product candidates for which we intend to seek approval as ~~biologic~~ **biologics** ~~products~~ may face competition sooner than anticipated. ~~With~~ **The Patient Protection and Affordable Act, as amended by** the ~~enactment of~~ **Healthcare and Education Reconciliation Act (the " ACA "), includes a subtitle called** the Biologics Price Competition and Innovation Act of 2009 ~~, or~~ **(" BPCIA ")** , **which created** an abbreviated **approval** pathway for ~~the approval of biosimilar~~ biological products **that are** ~~(both highly similar~~ **biosimilar** ~~and~~ **to or** interchangeable **with an FDA- licensed reference** biological ~~products) was created. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference~~ product. Under the BPCIA, an application for a **highly similar or " biosimilar " product may not be submitted to the FDA until four years following the date that the reference product was first approved by the FDA. In addition, the approval of a** biosimilar product ~~cannot~~ **may not** be ~~approved~~ **made effective** by the FDA until 12 years ~~after~~ **from** the ~~first licensure of~~ date ~~of~~ **on which** the reference product ~~licensed~~ **was first approved. During this 12- year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor' s own preclinical data and data from adequate and well- controlled clinical trials to demonstrate the safety, purity and potency of their product. We believe that any of our product candidates approved as biologics** under a BLA **should qualify** ~~. On March 6, 2015, the FDA approved the first biosimilar product under the BPCIA and on July 28, 2021, approved the first interchangeable biosimilar. A biological product submitted~~ for **the 12- year** ~~licensure under a BLA is eligible for a~~ period of exclusivity ~~that commences on the date of its licensure, unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under the BPCIA~~ . **However,** ~~There~~ **there** is a risk that this exclusivity could be shortened due to congressional action or otherwise, **or that the FDA will not consider our product candidates to be reference products for competing products,** potentially creating the opportunity for ~~biosimilar~~ competition sooner than anticipated. **Other aspects** ~~Additionally, this period~~ of ~~regulatory~~ **the BPCIA, some of which may impact the BPCIA** exclusivity **provisions** ~~does not apply to companies pursuing regulatory approval via their own traditional BLA , rather than via the abbreviated pathway. Most states~~ have **also been the subject** ~~enacted substitution laws that permit substitution~~ of **recent litigation** ~~only interchangeable biosimilars~~ . ~~The~~ **Moreover, the** extent to which a biosimilar, once approved, will be substituted for any ~~one of our~~ reference products ~~that may be approved~~ in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. ~~If~~ **Even if** we ~~fail to develop additional~~ **receive regulatory approval of our** product candidates, **we** ~~our commercial opportunity~~ will be **subject to extensive ongoing** ~~limited. Developing and obtaining~~ regulatory **obligations** ~~approval for~~ and ~~commercializing any~~ **continued regulatory review, which may result in significant** additional **expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our** product candidates ~~we identify will require substantial additional funding and is prone to the risks of failure inherent in medical product development~~ . **Any regulatory approvals** ~~We cannot provide you any assurance~~ that we **may** ~~will be able to successfully advance additional product candidates, if any, through the development process. Even if we~~ receive ~~FDA approval to market additional product candidates~~ for **our** ~~the treatment of the diseases we target, we cannot assure you that any such~~ product candidates will **require** ~~be successfully commercialized, widely accepted in~~ the ~~marketplace~~ **submission of reports to regulatory authorities and surveillance to monitor the safety and efficacy of the product candidate, may contain significant limitations related to use restrictions** ~~or~~ **for** ~~more effective than~~ **specified age groups, warnings, precautions or contraindications, and may include burdensome post- approval study or risk management requirements. For example,** ~~other~~ -- **the FDA may require a risk evaluation** ~~commercially available alternatives. If we are unable to successfully develop~~ and ~~commercialize additional~~ **mitigation strategy (" REMS") in order to approve our** product candidates, **which could entail requirements for a medication guide, physician training and communication plans** ~~our~~ - **or** ~~commercial opportunity~~ **additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or comparable foreign regulatory authorities approve our product**

candidates, our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export will be **subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable foreign regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration, as well as on- going compliance with current cGMPs and GCPs for any clinical trials that we conduct following approval. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMPs. If we or a regulatory authority discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facilities where the product is manufactured, a regulatory authority may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials, restrictions on the manufacturing process, warning or untitled letters, civil and criminal penalties, injunctions, product seizures, detentions or import bans, voluntary or mandatory publicity requirements and imposition of restrictions on operations, including costly new manufacturing requirements. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue and could require us to expend significant time and resources in response and could generate negative publicity. Existing regulatory policies may change, and additional government regulations may be enacted that could prevent,** ~~limited --~~ **limit or delay** ~~. Moreover, a failure in obtaining~~ regulatory approval of ~~additional~~ **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 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 lose any marketing approval that we** may have ~~a negative effect on the approval process of~~ **obtained and we may not achieve or sustain profitability. See** ~~other --~~ **the section titled " Business – Government Regulation – Healthcare Reform " for a more detailed description of healthcare reform measures that may prevent us from being able to generate revenue, attain profitability, or commercialize our** product candidates ~~of~~ **. Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third- party payors, patient organizations and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties. Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third- party payors, patient organizations and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct** ~~ours --~~ **our operations, including how we research, market, sell and distribute** ~~or~~ **our product candidates, if** ~~result in losing approval of any~~ approved ~~product candidate~~ . ~~If in~~ **See the section titled " Business – Government Regulation –** ~~the~~ **Other Healthcare Laws and Compliance Requirements " for a more detailed description of the laws that may affect our ability to operate. Ensuring that our internal operations and** future **business arrangements** ~~we are unable to establish U. S. or global sales and marketing capabilities or enter into agreements~~ with third parties ~~to sell~~ **comply with applicable healthcare laws** and ~~market~~ **regulations will involve substantial costs. If our operations are found to be in violation of any of these laws** ~~our --~~ **or** ~~product candidates, we~~ **any other governmental laws and regulations that** may ~~not~~ **apply to us, we may** be **subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from government- funded healthcare programs, integrity oversight and reporting obligations to resolve allegations of non- compliance, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly and time- consuming and may require significant personnel resources. Therefore, even if we are** successful in ~~commercializing~~ **defending against any such actions that may be brought against us,** our ~~product candidates~~ **business may be impaired. Even** if ~~they~~ **we** are **able** ~~approved, thus limiting our ability to generate any product revenue. We do not yet have a fully integrated commercial organization with all of the functions required to market, sell and distribute our product candidates that may receive regulatory approval. In order~~ to commercialize any product candidates ~~after approval~~ , **due** ~~we must build on a territory- by- territory basis marketing, sales, distribution, managerial and other non- technical capabilities or make arrangements with third parties~~ to **unfavorable pricing** ~~perform these services, and we may not be successful in doing so. If our product candidates receive regulatory~~ **regulations** ~~approval, we may decide to establish an~~ **and /** ~~internal sales or marketing team with technical expertise and supporting distribution capabilities to commercialize our --~~ **or** ~~product candidates, which will be expensive and time- consuming and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market. With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory- by- territory basis, 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. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. In March 2021, we entered into a license and supply agreement with Immedica, in which Immedica acquired the product rights for commercialization of pegzilarginase for certain territories outside the U. S. If we are unable to enter into or maintain such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and~~

we may incur significant additional losses. If we obtain approval to commercialize our product candidates outside of the United States, in particular in the European Union, a variety of risks associated with international operations could materially adversely affect our business. We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including: • different regulatory requirements for approval of drugs and biologics in foreign countries; • different processes and requirements to obtain adequate reimbursement for our approved therapies; • reduced protection for intellectual property rights; • unexpected changes in tariffs, trade barriers and regulatory requirements; • economic weakness, including inflation, or political instability in particular foreign economies and markets; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; • workforce uncertainty in countries where labor unrest is more common than in the United States; • production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and • business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods, fires or public health crises, pandemics, and epidemics, such as COVID- 19. Risks Related to Our Reliance on Third Parties We currently rely and will rely on third parties to conduct our ongoing and future planned clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials. We currently rely and will continue to rely on third parties to provide manufacturing and clinical development capabilities. We have agreements with and rely on third- party **coverage** CROs to conduct our ongoing and **reimbursement policies, we may** future planned clinical trials of pegtarviliase and pegzilarginase. We do not plan **be able** to **offer such** independently conduct clinical trials of our other product candidates **at competitive** . These agreements might terminate for a variety of reasons, including a failure to perform by the third parties -- **prices which** . If we need to enter into alternative arrangements, that would delay **seriously harm** our **business** product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our ongoing and future planned clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulatory standards, commonly referred to as good clinical practices 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. Other countries' regulatory agencies also have requirements for clinical trials with which we must comply . We **intend** also will be required to **seek** register ongoing clinical trials and post the results of completed clinical trials on a government- sponsored database, ClinicalTrials. gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our ongoing and future planned clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to complete our clinical trials, obtain, or may be delayed in obtaining, marketing approvals **approval** for **to market** our product candidates and will not be able to, or may be delayed in **both the United States and in selected foreign jurisdictions. If we obtain approval in one** our **or more foreign jurisdictions for** efforts to, successfully commercialize our product candidates . We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our product candidates , producing additional losses and depriving us of potential product revenue. We do not own or operate facilities for the manufacture of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. For example, we currently rely on third party contract manufacturing organizations to manufacture and supply nonclinical and clinical trial quantities of our product candidates pegtarviliase and pegzilarginase, and for additional pipeline product candidates. We also expect to continue to rely on such third parties to manufacture pegtarviliase for our clinical trials and to manufacture and supply clinical and commercial quantities of pegzilarginase. We rely, and expect to continue to rely, on third parties, for the manufacture of our product candidates for nonclinical studies and for our existing and future planned clinical trials. We also expect to rely on third parties for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will **be subject to rules** not have sufficient quantities of our product candidates or such quantities at an **and** acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance. Currently, third party manufacturers are supplying, and are expected to continue to supply, the drug substance requirements for our ongoing and planned clinical trials with pegtarviliase and pegzilarginase. If such third party manufacturers cannot supply us with sufficient amounts, pursuant to product requirements as agreed, we may be required to identify alternative manufacturers, which would lead us to incur added costs and delays in identifying and qualifying and obtaining any replacement. The formulation used in early studies may not be a final formulation for commercialization. If we are unable to demonstrate that our commercial scale product is comparable to the product used in clinical trials, we may not receive regulatory **regulations in** approval for that product without additional clinical trials. We have contracted with third party manufacturers for certain studies related to potential commercial scale manufacturing of pegtarviliase and pegzilarginase, but there is no guarantee that such studies, the **those jurisdictions. Our** transfer of technology to or any potential manufacturing at such facility **ability to** , will be completed successfully , on time, or at all. We also cannot guarantee that we will be able to make any required modifications within currently anticipated timeframes or that such modifications, if and when made, will obtain regulatory approval or that the new processes or modified processes will be successfully implemented by or transferred to any third- party contract suppliers within currently anticipated timeframes. These may require additional studies and may delay our clinical trials and / or commercialization. We expect to rely on third- party manufacturers or third- party strategic partners

~~for the manufacture of commercial supply of any product candidates for which our strategic partners or we obtain marketing approval. We may be unable to establish any additional agreements with third- party manufacturers, or to do so on acceptable terms. Even if we are able to establish agreements with third- party manufacturers on acceptable terms, such third- party manufacturers may have limited experience manufacturing pharmaceutical drugs for commercialization, and reliance on third- party manufacturers for the commercial supply of our products may expose us to various risks, including: • the possible noncompliance by the third party with regulatory requirements and quality assurance; • the possible breach of the manufacturing agreement by the third party; • the operations of such third parties could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of such party, the issuance of an FDA Form 483 notice or warning letter or other enforcement action by the FDA or other regulatory authority; • delays due to production shortages resulting from any events affecting supply or manufacturing capabilities domestically and abroad; • delays due to the malfunction or non- performance of manufacturing equipment resulting in failed manufacturing runs or the production of materials that do not meet quality standards; • the possible misappropriation of our proprietary information, including our trade secrets and know- how; and • the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us. Third- party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, or similar regulatory requirements outside the United States. Although we do not have day- to- day control over third- party manufacturers' compliance with these regulations and standards, we are responsible for ensuring compliance with such regulations and standards. Our failure, or the failure of our third- party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates, operating restrictions and criminal prosecutions, any of which would significantly and adversely affect supplies of our product candidates and our business. If a third- party manufacturer' s facilities do not pass a pre- approval inspection or do not have a cGMP compliance status acceptable to the FDA or a comparable foreign regulatory agency, our product candidate will not be approved. In addition, the process of manufacturing and administering our product candidates is complex and highly regulated. As a result of the complexities, our manufacturing and supply costs are likely to be higher than those at more traditional manufacturing processes and the manufacturing process is less reliable and more difficult to reproduce. Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. 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~~ **we may develop will depend in part** on ~~a timely~~ **the extent to which reimbursement for these product candidates** and ~~competitive basis~~ **related treatments will be available from government health administration authorities, private health insurers and other organizations** . ~~Failure of any future~~ **Government authorities and other** third- party ~~collaborators to successfully commercialize diagnostics or monitoring assays developed~~ **payors, such as private health insurers and health maintenance organizations, decide which medications they will pay** for **and establish reimbursement levels** ~~use with our therapeutic product candidates could harm our ability to commercialize these product candidates~~ . **Government authorities and** ~~We do not plan to internally develop diagnostics or monitoring assays, or Assays. As a result, we are dependent on the~~ **other** ~~efforts of our~~ third- party ~~strategic partners~~ **payors have attempted** to ~~successfully~~ **control costs by limiting coverage and the amount of reimbursement for particular medications. These entities may create preferential access policies for a competitor' s product, including a branded or generic / biosimilar product, over our products in an attempt to reduce their costs, which may reduce our** ~~commercialize~~ ~~---~~ **commercial opportunity. Additionally, if** any ~~needed Assays. Our strategic partners: • may not perform their obligations as expected; • may encounter production difficulties that could constrain the supply~~ of ~~the Assays; • may have difficulties gaining acceptance of the use of the Assays in the clinical community; • may not pursue commercialization of any Assays; • may elect not to continue or~~ **our** ~~renew commercialization programs based on changes in the strategic partners' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities; • may not commit sufficient resources to the marketing and distribution of such Assay~~ product candidates ~~,~~ **are approved** and **we are found to have improperly promoted off- label** ~~• may terminate their relationship with us. If Assays needed for use~~ **uses of those** ~~with our therapeutic~~ product candidates ~~fail to gain market acceptance~~ , **we may become subject to significant liability, which would materially adversely affect our business and financial condition. See the sections titled " Business – Government Regulation – Coverage and Reimbursement " and " Business – Other Government Regulation Outside of the United States – Regulation in the European Union " for a more detailed description of the government regulations and third party payor practices that may affect** our ability to **commercialize our** ~~derive revenues from sales of these therapeutic~~ product candidates ~~could be~~ **. We are subject to U. S. and certain foreign export and import controls, sanctions, embargoes, anti- corruption laws, and anti- money laundering laws and regulations. We can face criminal liability and other serious consequences for violations, which can** ~~harmed~~ ~~---~~ **harm our business** . ~~If~~ **We are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Controls, the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, and other state and national anti- bribery and anti- money laundering laws in the countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering,** ~~our~~ ~~--~~ **or** ~~strategic~~ **providing, directly or indirectly, improper payments or anything else of value to or from recipients in the public or private sector. We may engage third** ~~partners~~ ~~--~~ **parties** ~~fail~~ to ~~develop and commercialize~~ **sell our products outside** ~~these~~ ~~--~~ **the** ~~Assays~~ **United States** ,

~~it could~~ **to conduct clinical trials, and / or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. Governments outside the United States tend to impose strict price controls, which may** adversely affect ~~and delay the development or~~ **our** ~~commercialization~~ **revenue, if any. In some countries, particularly member states** of ~~our~~ **the EU, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a** therapeutic **. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. 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. To obtain coverage and reimbursement or pricing approvals in some countries, we or current or future collaborators may be required to conduct a clinical trial or other studies that compare the cost- effectiveness of our** product candidates ~~. We may not be successful in finding strategic partners for continuing development or commercialization of certain of our product candidates. We may seek~~ to ~~develop strategic partnerships for developing certain of our product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We also have entered into and expect to enter into future partnership agreements to commercialize pegzilarginase outside the United States, including through our licensing agreement with Immedica. We may not be successful in our efforts to establish such a strategic partnership or~~ other **available therapies in order** ~~alternative arrangements for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. In addition, we may be restricted under existing collaboration or license and development agreements from entering into future agreements with potential strategic partners. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such a transaction. If we are unable to reach agreements with suitable strategic partners on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, 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 fund development or commercialization activities on our own, or our existing or future partners are not able to adequately fund their development or commercialization activities pursuant to our arrangements, we may need~~ to obtain ~~additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our~~ **or maintain reimbursement** ~~product candidates and our~~ **or pricing approval** ~~business, financial condition, results of operations and prospects may be materially and adversely affected~~ . **Publication of discounts** ~~We may be subject to claims~~ by ~~third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property. Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims. In addition, while it is our policy to require our employees and contractors who may be involved in the 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 develops intellectual property that we regard as our own. Our and their assignment agreements may not be self- executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management. Risks Related to Government Regulation Our product candidates must be approved by the FDA pursuant to a BLA in the United States, by the EMA pursuant to an MAA, and by other comparable regulatory authorities outside the United States prior to commercialization. The process of obtaining marketing approvals, both in the United States and internationally, is expensive and takes many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval in Europe or another non- U. S. jurisdiction may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our~~ third- party **payors or** ~~strategic partners may not obtain approvals from regulatory~~ authorities ~~outside the United States~~ **may lead to further pressure** on ~~a timely basis, if at all. Approval by~~ the ~~FDA does not ensure approval by regulatory authorities in~~ **prices or reimbursement levels within the country of publication and** other countries ~~or jurisdictions, and approval by one regulatory authority outside the United States does not~~

ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA . **If reimbursement** Furthermore, the implementation of Brexit may disrupt the operation of any **product candidate approved** pre- and post- authorization clinical trial infrastructure and regulatory frameworks in Europe, as discussed further below. We may not be able to file for marketing approvals **is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be materially** and may not receive necessary approvals **adversely affected. Brexit could lead** to commercialize **legal uncertainty and potentially divergent national laws and regulations, including those related to the pricing of prescription pharmaceuticals, as the UK determines which EU laws to replicate or replace. If the UK were to significantly alter its regulations affecting the pricing of prescription pharmaceuticals, we could face significant new costs. A breakthrough therapy, fast track, or other expedited designation for** our product candidates **may** in any market. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not **lead** received approval to market any of **a faster development** our - **or** product candidates from regulatory **review** authorities in any jurisdiction. We have limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third- party CROs to assist us in this process. Securing marketing approval requires the submission of extensive nonclinical and clinical data and supporting information to regulatory authorities for - **or** each therapeutic indication to establish the product candidate' s safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional nonclinical , clinical or other studies. In addition, varying interpretations of the data obtained from nonclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may also cause delays in or prevent the approval of an **and** application. Approval of our product candidates..... s departure from the European Union, it no longer automatically complies with the standards of clinical efficacy, safety and chemistry control, and manufacture as applied by the European Medicines Directive. Applications submitted for marketing authorization under the centralized EMA procedure will no longer be automatically validated for authorization in the United Kingdom, and the benefit- risk assessments conducted by the United Kingdom may not be consistent with the EMA conclusions. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and / or the United Kingdom. In view of the current lack of detail and resolution with regard to the Brexit transition, we are unable to confidently predict the effects of such disruption to the regulatory framework in Europe, and as to how this may delay or impair any potential regulatory approvals, commercialization of any of our product candidates, and our ability to generate potential revenues. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired. Any Fast Track Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our **those** product candidates will receive marketing approval. We have received **may seek a breakthrough therapy,** Fast **fast** Track **track , or other designation for appropriate product candidates.** Designation **Designations** from **such as these are within the discretion of** the FDA **, or other comparable regulatory authorities. The receipt of a designation** for our **a** product candidate pegtarviliase for the treatment of Homocystinuria and for our product candidate pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency and may seek such designation for some or all of our other product candidates. If a drug or biologic is intended for the treatment of a serious or life- threatening condition and the drug or biologic demonstrates the potential to address unmet medical needs for this condition, the drug or biologic sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether or not **result** to grant this designation. Even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even though we have received Fast Track Designation for pegtarviliase for the treatment of Homocystinuria and for pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency, and even if we receive Fast Track Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs or biologics that have received Fast Track Designation have failed to obtain approval. The FDA may consider approval of our products through the use of the accelerated approval program, but such mechanism may not lead to a faster development or regulatory review or approval process. Even if we receive approval from the FDA under the accelerated approval program, if our confirmatory postmarketing trial does not verify clinical benefit, or if we do not comply with rigorous postmarketing requirements, the FDA may seek to withdraw the approval. Under the FDA' s accelerated approval program, the FDA may approve a drug or biologic for a serious or life- threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that is thought to predict clinical benefit but is not itself a measure of clinical benefit, or a biomarker that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug' s effect on a surrogate or intermediate clinical endpoint must be adequate and well

~~controlled as required by the FDC Act. If the FDA were to consider accelerated approval in the review of an application for any product candidates, the FDA may determine there is inadequate justification to support that our surrogate endpoint is reasonably likely to predict clinical benefit in patients. For drugs or biologics granted accelerated approval, post- marketing well-controlled, adequately powered confirmatory trials of sufficient duration are typically required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence, and the FDA could require that the trial be designed, initiated, and / or fully enrolled at the time of BLA submission. Moreover, the FDA may withdraw approval of our product candidate or indication approved under the accelerated approval pathway if, for example: • the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug; • other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use; • we fail to conduct any required post-approval trial of our product candidate with due diligence; or • we disseminate false or misleading promotional materials relating to the relevant product candidate. Recently, the accelerated approval pathway has come under scrutiny within the FDA and by Congress. The FDA has put increased focus on ensuring that confirmatory studies are conducted with diligence and, ultimately, that such studies confirm the benefit of the approved product, and Congress has considered various proposals to make changes to the accelerated approval pathway. The Food and Drug Omnibus Reform Act, or FDORA, was recently enacted, which included provisions related to the accelerated approval pathway. Pursuant to FDORA, the FDA is authorized to require a post-approval study to be underway prior to approval or within a specified time period following approval. FDORA also requires the FDA to specify conditions of any required post- approval study, which may include milestones such as a target date of study completion and requires sponsors to submit progress reports for required post- approval studies and any conditions required by the FDA not later than 180 days following approval and not less frequently than every 180 days thereafter until completion or termination of the study. FDORA enables the FDA to initiate criminal prosecutions for the failure to conduct with due diligence a required post- approval study, including a failure to meet any required conditions specified by the FDA or to submit timely reports. A Breakthrough Therapy designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval. We have received Breakthrough Therapy Designation from the FDA for our product candidate pegzilarginase for the treatment of Arginase 1 Deficiency and may seek such designation for some or all of our product candidates, including pegtarviliase. A Breakthrough Therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs, to treat a serious or life- threatening disease or condition, and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies with respect to one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs or biologics that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor can help to identify the most efficient path for development. Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe, after completing early clinical trials, that one of our product candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead determine not to make such designation. Even though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or even if we receive Breakthrough Therapy Designation for other product candidates, including pegtarviliase, or indications in the future, we may not experience a faster development process, review or approval compared to drugs or biologics~~ considered for approval under conventional FDA procedures and ~~such a designation~~ does not assure ultimate approval by the FDA. In addition, even ~~though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or~~ if one or more of our ~~other~~ product candidates ~~, including pegtarviliase,~~ qualify ~~as a Breakthrough Therapy~~ **under one of FDA' s designation programs** , the FDA may later decide that ~~such~~ **the** ~~product~~ **products** ~~candidates~~ no longer meet the conditions for qualification ~~. We may seek priority~~ **or decide that the time period for FDA** review ~~designation for~~ **or** ~~one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process. If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the application for such product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review of any future BLA we submit for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review designation to an application, so even if we believe an application for a particular product candidate is eligible for such designation, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in an expedited regulatory review or approval process or confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six- month review cycle or at all. Any product candidate for which we obtain marketing~~ approval will **not** be ~~subject to extensive post- approval marketing regulatory requirements~~ **shortened. See the section titled " Business – Government Regulation – Expedited Development** and **Review Programs "** ~~could be subject to post- approval marketing restrictions, requirements, or~~ **for** ~~withdrawal~~ **a more detailed description of the process for seeking expedited designations such as fast track or breakthrough therapy designations. Our ability to obtain and protect our patents and other proprietary rights is uncertain, exposing us to the possible loss of competitive advantage. We rely upon a combination of patents, trademarks, trade secret protection, confidentiality agreements and the Paragon Agreement to protect the intellectual property related to our programs and technologies and to prevent third parties** from **competing unfairly** ~~the market, and we may be subject to penalties if we fail to comply~~ with **us** ~~regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved~~ . Our ~~product candidates~~ **success depends in large part on our ability to obtain** and ~~the activities associated with~~ **maintain patent protection for our**

platform technologies, programs and their ~~development and commercialization, including their testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, cGMP, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by the FDA and other regulatory authorities, requirements regarding the distribution of samples to physicians and recordkeeping. The FDA closely regulates the post- approval marketing and promotion of drugs and biologics to ensure drugs and biologics are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use~~ **uses** ~~of their products and if we promote our product candidates beyond their approved indications, we may be subject to enforcement action for off- label promotion. Violations of the FDC Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws~~, as well as ~~state consumer protection laws. The FDA may also impose requirements for costly post- approval marketing studies or~~ **our ability** ~~clinical trials and surveillance~~ to **operate without infringing** ~~monitor the safety or efficacy of any approved product. In particular, certain of our product candidates, if approved, are expected to be dosed chronically, and therefore could require follow- up studies and close monitoring of our patients after regulatory approval has been granted, to establish broader, longer- term understanding of potential for adverse effects than is plausible for clinical research. These studies may be expensive and time- consuming to conduct and may reveal side effects or other harmful effects in patients that use our therapeutic products after they are~~ on ~~the market, which may result in the limitation or withdrawal of our~~ - **or violating** ~~drugs from the market. Alternatively, we may not be able to conduct such additional clinical trials, which might force us to abandon our efforts to develop or commercialize certain product candidates. Even if post- approval studies are not requested or required, after our products are approved and on the market, there~~ -- **the proprietary rights** ~~might be safety issues that emerge over time that require a change in product labeling or that require withdrawal~~ of **others** ~~the product from the market, which would cause our revenue to decline. If we fail to comply with any such post- approval regulatory requirements, approval for our products may be withdrawn, and product sales may be suspended~~. We ~~may not be able to regain compliance, or we may only be able to regain compliance after a lengthy delay, significant expense, lost revenues and damage to our reputation. In addition, later discovery of previously unknown adverse events or other problems with our product candidates, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including: • restrictions on~~ **own and have licensed rights** ~~such product candidates, manufacturers or manufacturing processes; • restrictions on the labeling or marketing of a product; • restrictions on product distribution or use; • requirements~~ to ~~conduct post- marketing studies or clinical trials; • warning or untitled letters; • withdrawal of any approved product from the market; • refusal to approve~~ pending **patent** applications ~~or supplements~~ **and expect** to ~~approved~~ **continue to file patent** applications **in** ~~that we submit; • recall of product candidates; • fines, restitution or disgorgement of profits or revenues; • suspension or withdrawal of marketing approvals; • refusal to permit~~ the **United States** ~~import or export of our product candidates; • product seizure; or • injunctions or the imposition of civil or criminal penalties. Non- compliance with European requirements regarding safety monitoring or pharmacovigilance,~~ and **abroad** ~~with requirements~~ related to ~~the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with European and certain U. S. state requirements regarding the protection of personal information can also lead to significant penalties and sanctions. Our relationships with customers 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. Healthcare providers, physicians and third- party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third- party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or~~ **our novel discoveries** ~~financial arrangements and relationships through which we market, sell and distribute any product candidates for which we obtain marketing approval. Restrictions under applicable U. S. federal and state healthcare laws and regulations include the following: • the federal Anti- Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an~~ **and technologies** ~~individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid; • the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment~~ that are ~~false~~ **important to** ~~or~~ **our** ~~fraudulent~~ **business. However, we may not be able to protect** ~~or~~ **our intellectual property rights throughout the world** ~~making a false statement to avoid, decrease or conceal an~~ **and** ~~obligation to pay money to~~ the **legal systems in certain countries may not favor enforcement** ~~federal government; • the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for~~ - **or protection** ~~executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; • HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission~~ of ~~individually identifiable health information; • federal law requires applicable manufacturers of covered drugs to report payments~~ **patents , trade secrets** and other **intellectual property. Filing** ~~transfers of value to physicians~~ , **prosecuting** ~~physician assistants, certain nurses,~~ and **defending patents** ~~teaching hospitals, which includes annual data collection and reporting obligations, with reported information disclosed~~ on ~~a searchable website on an annual basis; and • analogous state and foreign laws and regulations, such as state anti- kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors,~~

including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Other states require reporting of pricing information, including price increases. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of product candidates from government funded healthcare programs , such as Medicare **worldwide would be expensive** and Medicaid, and the curtailment or **our intellectual property rights** restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is 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. Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain. In the United States and some foreign jurisdictions **can be less extensive** , there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that **than those in** could prevent or delay marketing approval of our product candidates, restrict or regulate post- approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In the United States , **;** the Medicare Prescription Drug **reverse may also occur. As such** , Improvement, and Modernization Act of 2003, **we may not have patents in all countries** or **all major markets** the MMA, changed the way Medicare covers and pays **may not be able to obtain patents in all jurisdictions even if we apply** for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the **them** elderly and introduced a new reimbursement methodology based on average sales prices for physician- administered drugs . **Our competitors** In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved product candidates. While the MMA only applies to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result **operate** in **countries** a similar reduction in payments from private payors. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The ACA, among other things, also expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program and imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year. These reductions went into effect in 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2031, with the exception of a temporary suspension and reduction implemented under various COVID- 19 relief legislation through June 30, 2022, unless additional Congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1 % in 2022 to up to 4 % in the final fiscal year of this sequester. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On January 20, 2017, federal agencies with authorities and responsibilities under the ACA were **where we** directed to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the Tax Cuts and Jobs Act was signed into law, which eliminated certain requirements of the ACA, including the individual mandate. On June 17, 2021, the United States Supreme Court held that plaintiffs do not have standing to challenge the constitutionality of the individual mandate. It is unclear whether there will be additional challenges to the ACA. Additionally, on January 28, 2021, the President of the United States issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is uncertain how other such litigation or the healthcare measures of the United States administration will impact the ACA and our business. We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. For example, on September 9, 2021, the Biden administration published a wide- ranging list of policy proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. These initiatives recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the U. S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare

~~Part B and Part D, although this will only apply to high- expenditure single- source drugs that have been approved for at least 7 years (11 years for biologies). The negotiated prices will first become effective in 2026 and will be capped at a statutory ceiling price. The IRA will also, beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. In addition, the law eliminates the " donut hole " under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out- of- pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10 % of Part D enrollees' prescription costs for brand drugs below the out- of- pocket maximum and 20 % once the out- of- pocket maximum has been reached. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates. Legislative and regulatory proposals have been made to expand post- approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U. S. Congress of the FDA' s approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post- marketing testing and other requirements. Comprehensive tax reform bills could increase the tax burden on our orphan drug programs and adversely affect our business and financial condition. New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business and financial condition. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the 2017 Tax Cuts and Jobs Act, among others, reduced the orphan drug credit from 50 % to 25 % of qualifying expenditures. When and if we become profitable, this reduction in tax credits may result in an increased federal income tax burden on our orphan drug programs. On March 27, 2020, the Coronavirus Aid, Relief and Economic Security, or CARES Act, was enacted and modified certain portions of the 2017 Tax Cuts and Jobs Act, including with respect to the carryforward of net operating losses. Future changes in corporate tax rates, rules relating to the realization of net deferred tax assets, and other tax legislation could have a material impact on the value of our deferred tax assets, could result in a significant one- time charges, and could increase our future U. S. tax expense. Risks Related to Our Intellectual Property We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technology and product candidates. In particular, our success depends in large part on our ability, and our licensors' ability, to obtain and maintain~~ patent protection ~~in the United States~~ and ~~other~~ **can freely use our technologies and discoveries in such** countries ~~with respect~~ to ~~our proprietary technology and product candidates, including any diagnostic developed by us or a third- party strategic partner. We seek to protect our proprietary position by filing patent applications in~~ the **extent such** ~~United States and abroad related to our novel~~ technologies and **discoveries are publicly known** ~~product candidates and rely on our~~ **or** ~~licensors to obtain~~ **disclosed in countries where we do have** patent protection ~~for~~ **or** ~~our licensed intellectual property. Our patent portfolio includes patents and patent applications we own or we exclusively license from the University of Texas at Austin. This patent portfolio includes issued patents and~~ pending patent applications ~~covering compositions of matter and methods of use. The patent prosecution process is expensive and time- consuming, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner, or in all jurisdictions. We may choose not to seek patent protection for certain innovations and may choose not to pursue patent protection in certain jurisdictions, and under the laws of certain jurisdictions, patents or other intellectual property rights may be unavailable or limited in scope. It is also possible that we will fail to identify patentable aspects of our discovery and nonclinical and clinical development output before it is too late to obtain patent protection. Moreover, the risks pertaining to our patents and intellectual property rights also apply to the intellectual property rights that we license from third parties. In some circumstances, we do 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 third parties. We may also require the cooperation of our licensors in order to enforce the licensed patent rights, and such cooperation may not be provided. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business and the rights we have licensed may be reduced or eliminated. The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The U. S. Patent and Trademark Office, or U. S. PTO, has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. In addition, the laws of foreign jurisdictions may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain~~ . Our pending and future patent applications may not result in patents being issued **. Any issued patents may not afford sufficient protection of our programs or their intended uses against competitors, nor can there be any assurance** that ~~protect~~ **the patents issued will not be infringed, designed around, invalidated by third parties,** ~~our~~ **or** ~~technology or product candidates, in whole or in part, or which~~ effectively prevent others from commercializing competitive technologies **, products or programs. Even if these patents are**

granted, they may be difficult to enforce. Further, any issued patents that we may license or own covering our programs could be narrowed or found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad, including the United States Patent and **Trademark Office (" USPTO "). Further, if we encounter delays in our clinical trials or delays in obtaining regulatory approval, the period of time during which we could market our** product candidates **under** ~~. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our~~ patent protection **would be reduced. Thus, the patents that we may own and license may not afford us any meaningful competitive advantage** . In addition **to seeking** ~~, during prosecution of any patent application, the issuance of any~~ patents ~~based~~ **for some of our technology and programs, we may also rely** on **trade secrets, including unpatented know- how, technology** ~~an~~ **and other proprietary information,** ~~application may depend upon our ability~~ to **maintain** ~~generate additional nonclinical or~~ **our** ~~clinical data that supports the patentability of~~ **competitive position. Any disclosure, either intentional** ~~our~~ **or unintentional** ~~proposed claims. We may not be able to generate such data on a timely basis~~ , **by** ~~to the satisfaction of the U. S. PTO, or~~ **our employees** ~~at all. Moreover~~ , **the employees of third parties with whom** we **share our facilities or** ~~may be subject to a~~ third- party **consultants** ~~preissuance submission of prior art to the U. S. PTO or patent offices in foreign jurisdictions, or become involved in opposition, derivation, reexamination, inter partes review, post- grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates~~ and **vendors** ~~compete directly with us, without payment to us, or result in our inability to manufacture or commercialize product candidates without infringing third- party patent rights. 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. Even if our owned and licensed patent applications issue as patents, they may not issue in a form~~ that **we engage** ~~will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able~~ to ~~circumvent~~ **perform research, clinical trials** ~~our~~ **or** ~~owned or licensed patents by developing similar or alternative technologies or product candidates in a non- infringing manner. The issuance of a patent, while given the presumption of validity under the law, is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and product candidates, or limit the duration of the patent protection of our technology and product candidates. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after the first non- provisional filing in the patent family. 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 product candidates similar or identical to ours. Any inability on our part to adequately protect our intellectual property may have a material adverse effect on our business, operating results and financial position. 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, annuity fees and various other governmental fees on patents and / or applications will be due to be paid to the U. S. PTO and various governmental patent agencies outside the United States in several stages over the lifetime of the patents and / or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees. The U. S. PTO and various non- U. S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, we also rely on licensors to effect such payments with respect to the patents and patent applications that we in- license. Moreover, there are situations in which non- compliance 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. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business. Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business. Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture~~ **manufacturing activities** , ~~market and sell our~~ ~~or misappropriation~~ ~~product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference or derivation proceedings before the U. S. PTO and similar bodies in other jurisdictions. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We may also institute proceedings in courts or patent offices seeking decisions regarding the validity or scope of patents owned~~ by third parties ~~. It is also possible that we have failed~~ **(such as through a cybersecurity breach) of our trade secrets or proprietary information could enable competitors** to ~~identify relevant third-~~ **duplicate or surpass our technological achievements, thus eroding our competitive position in our market. In order to protect our proprietary technology and processes, we rely in** ~~party~~ **part** ~~patents~~ **on confidentiality agreements with** ~~or~~ **our collaborators** ~~applications. For example~~ , **employees** ~~applications filed before November 29~~ , ~~2000~~ **consultants, outside scientific collaborators** and ~~certain applications filed after that date that will~~ **sponsored researchers and other**

advisors. These agreements may not **effectively** ~~be filed outside the United States remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third- party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third- party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our products or the use of our products. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our product candidates and technology. 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. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent. A finding of infringement could~~ prevent **disclosure** ~~us from commercializing our product candidates or force us to cease some~~ of ~~our business operations, which could materially harm our business. Claims that we have misappropriated the~~ confidential information **and** ~~or trade secrets of third parties could have a similar negative impact on our business. We~~ may **not provide an adequate remedy in the event of unauthorized** ~~be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed~~ **disclosure of** confidential information ~~or trade secrets of third parties or that our employees, consultants or independent contractors have wrongfully used or disclosed alleged trade secrets of former or other employers~~. **We** ~~Many of our employees, independent contractors and consultants, including our senior management, have been previously employed or retained by universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Further, many~~ **may need to** ~~of our consultants are~~ **share** ~~currently retained by other biotechnology or~~ **our** ~~pharmaceutical companies and may be subject to conflicting obligations to these third parties. Although we try to ensure that our employees, consultants and independent contractors do not use the~~ proprietary ~~information or know- how of third parties in their work for us, and do not perform work for us that is in conflict with their obligations to another employer or any other entity, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise improperly used or disclosed confidential~~ information, including trade secrets **, with future business partners, collaborators, contractors and others located in countries at heightened risk of theft of trade secrets, including through direct intrusion by private parties or state actors and those affiliated with or controlled by state actors. In addition, while we undertake efforts to protect** ~~or~~ **our trade secrets and** other **confidential information from disclosure, others may independently discover trade secrets and** proprietary information, ~~of a former employer or other third parties. We may also be subject to claims that an~~ **and** ~~employee~~ **in such cases** , **we may not be able** ~~advisor, consultant, or independent contractor performed work for us that conflicts with that person's obligations~~ to ~~a third~~ **assert any trade secret rights against such** party **. Costly** ~~, such as an~~ **and time- consuming litigation could be necessary to enforce** ~~employer, and thus, that the third party has an~~ **and determine** ~~ownership interest in~~ the **scope** ~~intellectual property arising out~~ of ~~work performed~~ **our proprietary rights and failure to obtain** ~~for~~ ~~or~~ ~~us~~ **maintain trade secret protection could adversely affect our competitive business position** . ~~We~~ **Lastly, if our trademarks and trade names** are not **registered** ~~aware of any threatened~~ or **adequately protected** ~~pending claims related to these matters~~ , ~~but in the~~ **then** ~~future, litigation may be necessary to defend against such claims. In addition, while it is our policy to require our employees, independent contractors and consultants who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us,~~ we may **not** be **able** ~~unsuccessful in timely obtaining such an agreement with each party who in fact develops intellectual property that we regard as our own. Even if timely obtained, such agreements may be breached, and we may be forced~~ to **build name recognition in** ~~bring claims against third parties, or~~ **our markets** ~~defend claims they may bring against us, to determine the ownership~~ of **interest** ~~what we regard as our intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable personnel or intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. As a result, we may also elect to enter into license agreements in order to settle patent infringement claims or to resolve disputes prior to litigation, and any such license agreements may require us to pay royalties and other fees that could be significant. Such an~~ **and** ~~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. The illegal distribution and sale by third parties of counterfeit versions of our products or stolen products could have a negative impact on our reputation and business. Third parties might illegally distribute and sell counterfeit or unfit versions of our approved products, if any, which do not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit drug~~ may be ~~at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit drugs sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in- transit, which are not properly stored and which are sold through unauthorized channels, could~~ adversely **affected** ~~impact patient safety, our reputation and our business. Any lawsuits relating to infringement of intellectual property rights necessary to defend ourselves or enforce our rights will be costly and time consuming, and could be unsuccessful. Because competition in our industry is intense, competitors may infringe or otherwise violate our issued patents, patents of our licensors or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging, among other claims, that we infringe their patents. In addition, in a patent infringement proceeding there are many~~

~~grounds upon which a party may assert invalidity or unenforceability of a patent, and a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. Litigation is uncertain and we cannot predict whether we would be successful in any such litigation. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial, managerial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial, managerial and other resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our business. 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. Intellectual property disputes could cause us to spend substantial resources and distract our personnel from their normal responsibilities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and / or 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 market price of our common stock. In some cases, we may choose not to pursue litigation against those that have infringed on our patents, or used them without authorization, due to the associated expenses and time commitment of monitoring these activities. If we fail to protect or to enforce our intellectual property rights successfully, our competitive position could suffer, which could harm our results of operations.~~ We may not be successful in obtaining or maintaining necessary rights ~~for~~ **to** our **programs** ~~development pipeline~~ through acquisitions and in-licenses. ~~Presently we have rights to intellectual property to develop our product candidates, including patents and patent applications we own or exclusively license from the University of Texas at Austin.~~ Because our **development** programs **currently do and** may **in the future** ~~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 **third- party** proprietary rights. We may be unable to acquire or in- license any compositions, methods of use, processes or other third- party intellectual property rights from third parties that we identify as necessary for our **programs** ~~product candidates~~. The licensing and acquisition of third- party intellectual property rights is a competitive area, and a number of more established companies **may pursue** ~~are also pursuing~~ strategies to license or acquire third- party intellectual property rights that we may consider attractive **or necessary**. These established companies may have a competitive advantage over us due to their size, ~~cash~~ **capital** resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third- party intellectual property rights on terms that would allow us to make an appropriate return on our investment **or at all**. If we are unable to successfully obtain rights to required third- party intellectual property rights **or maintain the existing intellectual property rights we do obtain**, **we may have to abandon development of the relevant program, which could have a material adverse effect on** our business, financial condition **, results of operations,** and prospects **. While we normally seek to obtain the right to control prosecution, maintenance and enforcement of the patents relating to our programs, there may be times when the filing and prosecution activities** for ~~growth~~ **patents and patent applications relating to our programs are controlled by our current and future licensors or collaboration partners. If any of our current and future licensors or collaboration partners fail to prosecute, maintain and enforce such patents and patent applications in a manner consistent with the best interests of our business, including by payment of all applicable fees for patents covering our product candidates, we** could ~~suffer. If~~ **lose our rights to the intellectual property or our exclusivity with respect to those rights, our ability to develop and commercialize those product candidates may be adversely affected and** we **may not be able to prevent competitors from making, using and selling competing products. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed to and from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensees, our current and future licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution. Our current and future licensors may rely on third- party consultants or collaborators or on funds from third parties such that our current and future licensors** are not **the sole and exclusive owners of the patents we in- license. If other third parties have ownership rights to our current and future 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. It is possible that we may be unable to obtain licenses at a reasonable cost or on reasonable terms, if at all. 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 redesign our technology, programs, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business, financial condition, results of operations, and prospects significantly. We cannot provide any assurances that third- party patents do not exist which might be enforced against our current technology, manufacturing methods, programs, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and / or other forms of compensation to third parties, which could be significant. Disputes may arise between us and our current and future licensors regarding intellectual property subject to a license agreement, including: the scope of rights granted under the license agreement and other interpretation- related issues; whether and**

the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; our right to sublicense patents and other rights to third parties; our right to transfer or assign the license; the inventorship and ownership of inventions and know- how resulting from the joint creation or use of intellectual property by our current and future licensors and us and our partners; and the priority of invention of patented technology. We may be subject to patent infringement claims or may need to file claims to protect our intellectual property, which could result in substantial costs and liability and prevent **us from commercializing our potential products. Because the intellectual property landscape in the biotechnology industry is rapidly evolving and interdisciplinary, it is difficult to conclusively assess our freedom to operate and guarantee that we can operate without infringing on or violating third party rights. If certain of our product candidates are ultimately granted regulatory approval, patent rights held by third parties, if found to be valid and enforceable, could be alleged to render one or more of our product candidates infringing. If a third party successfully brings a claim against us, we may be required to pay substantial damages, be forced to abandon any affected product candidate and / or seek a license from the patent holder. In addition, any intellectual property claims (e. g. patent infringement or trade secret theft) brought against us, whether or not successful, may cause us to incur significant legal expenses and divert the attention of our management and key personnel from other business concerns. We cannot be certain that patents owned or licensed by us will not be challenged by others in the course of litigation. Some of our competitors may be able to sustain the costs of complex intellectual property 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 funds and on the market price of our common stock. Competitors may infringe or otherwise violate our patents, trademarks, copyrights or other intellectual property. To counter infringement or other violations, we may be required to file claims, which can be expensive and time- consuming. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. In addition, in a patent infringement proceeding, a court or administrative body may decide that one or more of the patents we assert is invalid or unenforceable, in whole or in part, construe the patent' s claims narrowly or refuse to prevent the other party from using the technology at issue on the grounds that our patents do not cover the technology. Similarly, if we assert trademark infringement claims, a court or administrative body 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 such a case, we could ultimately be forced to cease use of such marks. In any intellectual property litigation, even if we are successful, any award of monetary damages or other remedy we receive may not be commercially valuable. Further, we may be required to protect our patents through procedures created to attack the validity of a patent at the USPTO. An adverse determination in any such submission or proceeding could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position. 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. In addition, if our programs are found to infringe the intellectual property rights of third parties, these third parties may assert infringement claims against our future licensees and other parties with whom we have business relationships and we may be required to indemnify those parties for any damages they suffer as a result of these claims, which may require us to initiate or defend protracted and costly litigation on behalf of licensees and other parties regardless of the merits of such claims. If any of these claims succeed, we may be forced to pay damages on behalf of those parties or may be required to obtain licenses for the products they use. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other legal proceedings relating to our intellectual property rights, there is a risk that some of our confidential information could be compromised by** disclosure **during this type** of **litigation** ~~our~~ **or other proceedings. We may be subject to claims that we have wrongfully hired an employee from a competitor or that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties. As is common in the biotechnology industry, in addition to our employees, we engage the services of consultants to assist us in the development of our programs. Many of these consultants, and many of our employees, were previously employed at, or may have previously provided or may be currently providing consulting services to, other biotechnology or pharmaceutical companies including our competitors or potential competitors. We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged** trade secrets **or other confidential information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know- how or trade secrets of others in their work for us, we may become subject to claims that we caused** ~~and~~ **an employee to breach the terms of his or her non-competition or non- solicitation agreement, or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or** other proprietary information ~~, the value~~ of **a former employer** ~~our~~ **or** ~~technology and product candidates~~ **competitor. While we may litigate to defend ourselves against these claims, even if we are successful, litigation** could **result in substantial costs and could** be **a distraction** ~~significantly diminished. We rely on trade secret protection~~ to ~~protect~~ **management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies** ~~our~~ **or features** ~~interests in proprietary know- how and in processes~~ that are ~~unpatentable~~ **essential to** ~~or~~ **our programs, if such technologies** ~~for~~ **or features** ~~which patents~~ are ~~difficult~~ **found** to **incorporate** ~~obtain or enforce. We may not be able to protect our~~ **or be derived from the** trade secrets ~~adequately. We have a policy of requiring our consultants, advisors and strategic partners to enter into confidentiality agreements and our~~

~~employees to enter into invention, non- disclosure and non- compete agreements. However, no assurance can be given that we have entered into appropriate agreements with all parties that have had access to our trade secrets, know- how~~ or other proprietary information **of the former employers. Moreover** , **any** ~~or that~~ such ~~agreements will provide~~ **litigation or the threat thereof may adversely affect our reputation, our ability to** ~~for~~ **form strategic alliances** ~~a meaningful protection of our~~ **or sublicense** ~~trade secrets, know- how or~~ **our** ~~other proprietary information in the event~~ **rights to collaborators, engage with scientific advisors or hire employees or consultants, each** of **which would have** ~~any~~ **an** ~~unauthorized use~~ **adverse effect on** ~~or~~ **our business** ~~disclosure of information. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult~~ , ~~expensive~~ **results of operations** and **financial condition** ~~time- consuming, and the outcome is unpredictable~~ . Even if we are successful in ~~prosecuting~~ **defending against** such claims, **litigation** ~~any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. Furthermore, although we seek to preserve the integrity and confidentiality of our data, trade secrets and know- how by maintaining physical security of our premises and physical and electronic security of our information technology systems, it is also possible that our trade secrets, know- how or other proprietary information~~ could ~~be obtained by third parties as a~~ result ~~of breaches of such systems. Any disclosure of confidential information into the public domain or to third parties could allow our competitors to learn our trade secrets and use the information~~ in ~~competition against us. In addition, others may independently discover or develop our trade secrets and proprietary information or substantially~~ **substantial costs** ~~equivalent techniques or may design around our intellectual property rights. Any action to enforce our rights is likely to be time consuming~~ and ~~expensive, and may ultimately~~ be ~~unsuccessful, or may result in~~ a **distraction to management** ~~remedy that is not commercially valuable~~ . **Changes to patent** ~~These risks are accentuated in foreign countries where~~ laws ~~or law enforcement practices may not protect proprietary rights as fully as~~ in the United States **and other jurisdictions** ~~or Europe. Any unauthorized disclosure of our trade secrets or confidential information~~ could ~~harm~~ **diminish the value of patents in general, thereby impairing** our **ability** ~~competitive position. We may not be able~~ to protect our ~~intellectual property rights throughout the world. Filing, prosecuting and defending patents on all of our product~~ **products** ~~candidates throughout~~ **. Changes in either** the ~~world would be prohibitively expensive, and our~~ patent ~~rights~~ **laws or interpretation of patent laws** in ~~some countries outside~~ the United States ~~can be less extensive than~~ **, including patent reform legislation such as** ~~those~~ **the** ~~in~~ **Leahy- Smith America Invents Act (** the **" Leahy- Smith Act ") could increase the uncertainties and costs surrounding the prosecution of our owned and in- licensed patent applications and the maintenance, enforcement or defense of our owned and in- licensed issued patents. The Leahy- Smith Act includes a number of significant changes to** United States **patent law** . ~~The~~ **These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost- effective avenues for competitors to challenge the validity of patents, and enable third- party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO- administered post- grant proceedings, including post- grant review, inter partes review and derivation proceedings. Assuming that other** requirements for patentability **are met** ~~may differ in certain countries~~ , ~~particularly developing countries~~ **prior to March 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. After March 2013, under the Leahy- Smith Act, the United States transitioned to a first- to- file system in which, assuming that the other statutory 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. As such, the Leahy- Smith 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, financial condition, results of operations and prospects** . In addition, the **patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. U. S. Supreme Court and U. S. Court of Appeals for the Federal Circuit rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations, including in the antibody arts. For example, the United States Supreme Court in Amgen, Inc. v. Sanofi (Amgen) recently held that Amgen' s patent claims to a class of antibodies functionally defined by their ability to bind a particular antigen were invalid for lack of enablement where the patent specification provided twenty- six exemplary antibodies, but the claimed class of antibodies covered a " vast number " of additional antibodies not disclosed in the specification. The Court stated that if patent claims are directed to an entire class of compositions of matter, then the patent specification must enable a person skilled in the art to make and use the entire class of compositions. This decision makes it unlikely that we will be granted U. S. patents with composition of matter claims directed to antibodies functionally defined by their ability to bind a particular antigen. Even if we are granted claims directed to functionally defined antibodies, it is possible that a third party may challenge our patents, when issued, relying on the reasoning in Amgen or other recent precedential court decisions. Additionally, there have been proposals for additional changes to the patent** laws of ~~some~~ **the United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. 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 patent rights and our ability to protect, defend and enforce our patent rights in the future. Geopolitical instability in the United States and in** foreign countries **could increase** ~~do not protect intellectual property rights to~~ the **uncertainties** ~~same extent as federal~~ and ~~state laws in~~ **costs surrounding the prosecution or maintenance of patent applications and the maintenance, enforcement or defense of issued patents. For example,** the United States **and foreign government actions related to Russia' s invasion of 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 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 that have citizenship or nationality in, are registered in, or have predominately primary place of business or profit- making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation . Consequently, we ~~may~~ **would** not be able to prevent third parties from practicing our inventions in **Russia** ~~all countries outside the United States,~~ 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. In addition, a European Unified Patent Court (" UPC ") entered into force on June 1, 2023. The UPC is a common patent court that hears patent infringement and revocation proceedings effective for member states of the EU. This could enable third parties to seek revocation of a European patent in a single proceeding at the UPC rather than through multiple proceedings in each of the jurisdictions in which the European patent is validated. Although we do not currently own any European patents or applications, if we obtain such patents and applications in the future, any such revocation and loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and products. Moreover, the controlling laws and regulations of the UPC will develop over time, and may adversely affect our ability to enforce or defend the validity of any European patents we may obtain. We may decide to opt out from the UPC any future European patent applications that we may file and any patents we may obtain. If certain formalities and requirements are not met, however, such European patents and patent applications could be challenged for non- compliance and brought under the jurisdiction of the UPC. We cannot be certain that future European patents and patent applications will avoid falling under the jurisdiction of the UPC, if we decide to opt out of the UPC. Obtaining and maintaining patent protection depends on compliance with various procedural, document submissions, 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 patents and / or patent applications 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 also require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. 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. Non- compliance 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. If we fail to maintain the patents and patent applications covering our programs, our competitive position would be adversely affected. We may not identify relevant third- party patents or may incorrectly interpret the relevance, scope or expiration of a third- party patent, which might adversely affect our ability to develop and market our products. We cannot guarantee that any of our patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third- party patent and pending application in** the United States **and abroad that is relevant to or necessary** ~~or~~ **for** ~~other~~ -- **the commercialization of our product candidates in any** ~~jurisdictions~~ - **jurisdiction** . ~~As part~~ **The scope** of ~~ordinary course~~ **a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent' s** prosecution ~~and maintenance activities~~ **history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect. For example** , we **may incorrectly** determine **that our products are not covered by a third- party patent or may incorrectly predict** whether ~~to seek~~ **a third- party' s pending application will issue with claims of relevant scope. Our determination of the expiration date of any** patent **in** ~~protection outside~~ the United States **or abroad that we consider relevant may be incorrect. Our failure to identify** and **correctly interpret relevant patents may negatively impact our ability to develop and market our products. 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, 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 issued patents or our pending applications, or that we 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 patent applications or patents,** which **could require us** ~~countries. This also applies~~ to **obtain rights to issued** patents ~~we~~ **covering such technologies. 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 former employees, collaborators or other third parties** have ~~acquired~~ **an interest in** ~~or~~ **our** ~~in~~ **patents or other intellectual property as an inventor or co** - ~~licensed~~ **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, 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 programs 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, 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. Our current and future licensors may have relied on third- party consultants or collaborators or on funds from third parties ~~. In some cases , this means~~ **such as the U. S. government, such** that ~~we, or~~ **our** ~~our predecessors in interest or~~ licensors **are not the sole and exclusive owners** of **the** patents ~~within our portfolio, have sought patent protection in a limited number of countries for patents covering our product candidates. Competitors may use our technologies in jurisdictions where~~ we ~~have not pursued and 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~~ in **- licensed** ~~the United States . These products may compete with our products in jurisdictions where we do not have any issued patents and, even in jurisdictions where we have or~~ **For example** ~~are able to obtain issued patents ,~~ **certain** ~~our patent claims or other~~ intellectual property **we license** ~~rights may not be effective or sufficient to prevent them~~ from ~~so 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 patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost 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. In addition, certain countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if our patents are infringed or if we are compelled to grant a license to our patents to a third party, which could materially diminish the value of those patents. In addition, there may be patent law reforms in foreign jurisdictions that could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents in those foreign jurisdictions. This could limit our potential revenue opportunities. Accordingly, our efforts to obtain, register, and enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license. Moreover, patent protection must ultimately be sought on a country- by- country basis, which is an expensive and time- consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries. If we breach any of the agreements under which we license patent rights to use, develop and commercialize our product candidates or our technologies from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business. We are a party to license agreements under which we are granted rights to intellectual property that are important to our business and we expect that we may need to enter into additional license agreements in the future. In December 2013, our wholly owned subsidiaries AECase, Inc. and AEMase, Inc. each entered into an exclusive, worldwide license agreement, including the right to grant sublicenses, with~~ the University of Texas at Austin ~~for certain intellectual property owned by the University of Texas at Austin related to our program candidates related to cystinase and methioninase. In January 2017, we and the University of Texas at Austin entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including our program candidates under the pegtarviliase and Cystinuria programs. The intellectual property licensed under the Restated License~~ includes inventions that were made with U. S. government support. The U. S. government therefore has certain rights in such inventions under the applicable funding agreements and under applicable law. **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. Patent terms may be inadequate to protect the competitive position of our product candidates for an adequate amount of time. Patents have a limited lifespan.** In ~~addition~~ **the United States** , ~~we~~ **if all maintenance fees** are ~~subject to~~ **timely paid, the natural expiration of** a ~~requirement~~ **patent is generally 20 years from its earliest United States non- provisional filing date. Various 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 products, including generics or biosimilars. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product 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. Our current or future licensors may retain certain rights under the relevant agreements with us, including 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 our licensors limit their use of the technology to these uses, and we could incur substantial expenses to enforce our rights to our licensed technology in the event of misuse. We rely on collaborations and licensing arrangements with third parties, including our arrangement with Paragon. If we are unable to maintain these collaborations or licensing arrangements, or if these collaborations or licensing arrangements are not**

successful, our business could be negatively impacted. We currently rely on our collaborations and licensing arrangements with third parties, including Paragon, for a substantial portion of our discovery capabilities and in-licenses. Collaborations or licensing arrangements that **we enter into may not be successful, and any success will depend heavily on the efforts and activities of such collaborators or licensors. If any of our collaborators or licensors experiences delays in performance of, or fails to perform its obligations under their agreement with us, disagrees with our interpretation of the terms of such agreement or terminates their agreement with us, the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement and development timeline could be adversely affected. If we fail to comply with any of the obligations under our collaborations or license agreements, including payment terms and diligence terms, our collaborators or licensors may have the right to terminate such agreements, in which event we may lose intellectual property rights and may not be able to develop, manufacture, market or sell** the products covered by ~~the applicable patents that are sold or~~ **our** ~~used in the United States must be manufactured substantially in the United States unless a written waiver is obtained in advance from the U. S. government. The Restated License obligates us to make certain payments at the achievement of certain milestones and at regular intervals throughout the life of the license. The University of Texas at Austin may terminate the Restated License under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense). Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Any other licenses or other intellectual property~~ agreements ~~we may enter into may impose various diligence, milestone payment, royalty and other obligations on us. If disputes arise between us and our~~ **or may** ~~licensor or if we fail to comply with our obligations under current or future intellectual property agreements, potentially giving our counterparties the right to terminate these agreements, we might not be able to develop, manufacture or market any product that is covered by the agreement or~~ face other penalties under **our** ~~the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these~~ agreements ~~or reduction or elimination of~~ **. Our collaborators and licensors may also fail to properly maintain** ~~our~~ **or defend** ~~rights under these~~ **the** ~~agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important~~ intellectual property **we have** ~~or technology. The loss of any one of our current licenses, or any other license~~ **licensed from** ~~we may acquire in the~~ **them** ~~future~~ , **if required** ~~could prevent or impair our ability to successfully develop and commercialize the affected product candidates and thus materially harm our business, prospects, financial condition and results of operations. Intellectual property rights do not necessarily address all potential threats to our competitive advantage. The degree of future protection afforded~~ by **our agreement with them, or even infringe upon,** our intellectual property rights ~~is uncertain because~~ **, leading to the potential invalidation of our** intellectual property ~~rights have~~ **or subjecting us to** ~~limitations~~ **litigation or arbitration** , **any of which would be time-consuming** and **expensive and could harm our ability to commercialize our product candidates. In addition, collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our programs and products if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours. As part of our strategy, we plan to evaluate additional opportunities to enhance our capabilities and expand our development pipeline or provide development or commercialization capabilities that complement our own. We** may not ~~adequately protect~~ **realize the benefits of such collaborations, alliances** ~~our~~ **or licensing arrangements. Any of these relationships may require us to incur non- recurring and other charges, increase our near and long- term expenditures, issue securities that dilute our existing stockholders or disrupt our management and** business **. We may face significant** ~~, provide a barrier to entry against our competitors~~ **competition** ~~or potential competitors~~ **in attracting appropriate collaborators** , ~~or permit us~~ **and more established companies may also be pursuing strategies** to ~~maintain~~ **license** ~~our~~ **or acquire** ~~competitive advantage. Moreover, if a~~ third ~~-~~ party ~~has~~ intellectual property rights that **we consider attractive. These companies may have a competitive advantage** ~~cover~~ **over us due to** ~~the~~ **their** ~~practice of~~ **size, financial resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign** ~~our~~ **or license rights to us. Whether we reach a definitive agreement for a collaboration will depend upon, among other things, our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator' s evaluation of a number of factors. Collaborations are complex and time- consuming to negotiate, document and execute. In addition, consolidation among large pharmaceutical and** ~~technology~~ **biotechnology companies has reduced the number of potential future collaborators. We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop** ~~or~~ **our** product candidates ~~, we may not be able to fully exercise or extract value from our~~ **or bring** ~~intellectual property rights. The following examples are illustrative: • others may be able to make compounds that are similar to our product candidates but that are not covered by the~~ **them** ~~claims of~~ **to market. We currently rely, and plan to rely in** the **future,** ~~patents that we own~~ **on third parties to conduct and support** ~~or~~ **our** ~~license or may develop drug candidates for~~ **preclinical studies and clinical trials. If** ~~the~~ **these third parties** ~~diseases our drug candidates seek to treat that~~ do not ~~infringe our intellectual property~~ **properly and** ~~rights, but which perform better or are more successful~~ **successfully carry out** ~~than our drug candidates; • drug candidates covered by issued patents and other intellectual property that we hold may prove to be ineffective for~~ their ~~intended treatment~~ **contractual duties** or **meet expected deadlines,** we may not **be able to** obtain regulatory approval **of or commercialize our product candidates. We have utilized and plan to**

continue to utilize and depend upon independent investigators and collaborators, such as medical institutions, CROs, contract testing labs and strategic partners, to conduct and support our preclinical studies and clinical trials under agreements with us. We will rely heavily on these third parties over the course of our preclinical studies and clinical trials, and we control only certain aspects of their activities. As a result, we will have less direct control over the conduct, timing and completion of these preclinical studies and clinical trials and the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Nevertheless, we are responsible for **ensuring that each of our studies and trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third- party contractors and CROs are required to comply with GCP regulations, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our programs in clinical development. If we or any of these third parties fail to comply with applicable GCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority,** such ~~drug candidates; • we~~ **regulatory authority will determine that any of** ~~or~~ **our** ~~our licensors~~ **clinical trials comply with GCP regulations. In addition,** ~~or~~ **our** ~~collaborators might~~ **clinical trials must be conducted with products produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. Any third parties conducting our clinical trials will** not **be 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 programs. These third parties may be involved in mergers, acquisitions or similar transactions and may** have **relationships** ~~been the first to make the inventions covered by an issued patent or pending patent application that we own or license; • we or our licensors or collaborators might not have been the first to file patent applications covering an invention; • others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing or misappropriating our intellectual property rights; • pending patent applications that we own or license may not lead to issued patents; • issued patents that we own or license may not provide us~~ with ~~any competitive advantages~~ **other commercial entities** , **including** ~~or may be narrowly construed or held invalid or unenforceable, as a result of legal challenges by~~ our competitors ~~; • our competitors might~~ **, for whom they may also be** ~~conduct~~ **conducting** ~~research and~~ **clinical trials or other product** development activities ~~in countries where we~~ **, which could negatively affect their performance on our behalf and the timing thereof and could lead to products that compete directly or indirectly with our current or future product candidates. If these third parties** do not ~~have patent rights and then use~~ **successfully carry out their contractual duties or obligations or meet expected deadlines, if** ~~the~~ **they** ~~information learned from~~ **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 or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. In addition, we currently rely on foreign CROs and CMOs, including WuXi Biologics, and will likely continue to rely on foreign CROs and CMOs in the future. Foreign CMOs may be subject to U. S. legislation, including the proposed BIOSECURE bill, trade restrictions and other foreign regulatory requirements which could increase the cost or reduce the supply of material available to us, delay the procurement or supply of** such **material** ~~activities to develop competitive products for~~ **or** ~~sale in our major commercial markets; • we may not develop or in- license additional proprietary technologies that are patentable; and • the patents of others may~~ have an adverse effect on our **ability to secure significant commitments from governments to purchase our potential therapies. For example, the biopharmaceutical industry in China is strictly regulated by the Chinese government. Changes to Chinese regulations or government policies affecting biopharmaceutical companies are unpredictable and may have a material adverse effect on our collaborators in China which could have an adverse effect on our** business **, financial condition** ~~. Any of these events could significantly harm our business~~ , results of operations and prospects. **Evolving** ~~Changes~~ **changes** in **China' s public health** ~~patent law could diminish the value of patents in general~~ , **economic** ~~thereby impairing our ability to protect our products~~ , **political,** and **social conditions and** ~~recent patent legislation could increase~~ the ~~uncertainties~~ **uncertainty around China' s relationship** ~~and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. As is the case~~ with other **governments** ~~biotechnology companies~~ , **such as** ~~our success is heavily dependent on patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time- consuming and inherently uncertain. Further,~~ the United States **and the UK, could also negatively impact** ~~has recently enacted patent reform legislation. In addition to increasing uncertainty with regard to~~ our ability to ~~obtain patents~~ **manufacture our product candidates for our planned clinical trials or have an adverse effect on our ability to secure government funding, which could adversely affect our financial condition and cause us to delay our clinical development programs. We currently rely and expect to rely** in the future ~~, this has created greater uncertainty with respect to the value of patents, once obtained. Depending~~ on ~~decisions by~~ the ~~U. S. Congress~~ **use of manufacturing suites in third- party facilities or on third parties to manufacture our product candidates** , ~~the federal courts,~~ and **we may rely on third parties to produce** ~~the U. S. PTO, the laws~~ and ~~regulations governing patents~~ **process our products, if approved. Our business** could ~~change in unpredictable ways that would weaken~~ **be adversely affected if we are unable to use third- party manufacturing suites** ~~our~~ **or if** ~~ability to obtain new patents or to enforce our existing patents and patents that we might obtain in~~ the ~~future~~ **third- party manufacturers encounter difficulties in production** . **We** ~~If we~~ do not **currently own any facility that may be used as our clinical** ~~obtain patent term extensions under the Hatch- Waxman Act and~~

~~similar legislation, thereby not extending the term of our~~ **or** ~~marketing exclusivity for~~ **commercial manufacturing and processing facility and must currently rely on CMOs to manufacture** our product candidates ~~, our business may be materially harmed. Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one of the U. S. patents covering each of such approved product (s) or the use thereof may be eligible for up to five years of patent term restoration. Patent term extension allows a maximum of one patent to be extended per FDA- approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates, if any. Nevertheless, we may not be granted patent term extension either in the United States or in any foreign country because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. In addition, if a patent we wish to extend is owned by another party and licensed to us, we may need to obtain approval and cooperation from our licensor to request the extension. If we are unable to obtain patent term extension or restoration, or the term or scope 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 our revenue could be reduced, possibly materially~~ . We have not yet ~~registered~~ **caused** our **product candidates** ~~trademarks in all of our potential markets, and failure~~ to ~~secure~~ **be manufactured on a commercial scale and may not be able to do so for any of our programs, if approved. We currently have a sole source relationship for our supply of** ~~those~~ -- **the** ~~registrations~~ **SPY001 program. If there should be any disruption in such supply arrangement, including any adverse events affecting our sole supplier, it** could **have a negative effect on the clinical development of our programs and other operations while we work to identify and qualify an alternate supply source. We may not control the manufacturing process of, and may be completely dependent on, our contract manufacturing partners for compliance with cGMP requirements and any other regulatory requirements of the FDA or comparable foreign regulatory authorities for the manufacture of our product candidates. Beyond periodic audits, we have limited control over the ability of our CMOs 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 approval in the future, we may need to find alternative manufacturing facilities, which would require the incurrence of significant additional costs, delays, and materially** adversely affect our **ability to develop, obtain regulatory approval for or market our product candidates, if approved. Similarly, our failure, or the failure of our CMOs, 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** . ~~We attempt~~ **Moreover, our CMOs may experience manufacturing difficulties due** to ~~protect~~ **resource constraints, supply chain issues,** ~~our~~ **or** ~~pharmaceutical developments, services, and~~ **as a result of labor disputes or unstable political environments. If any CMOs on which we will rely fail to manufacture quantities of our** ~~products~~ **product candidates at quality levels necessary to meet regulatory requirements** ~~under trademark laws. However, our trademark applications may not be allowed for registration, and registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an~~ **and** ~~opportunity~~ **at a scale sufficient** to ~~respond~~ **meet anticipated demand at a cost that allows us** to ~~those rejections~~ **achieve profitability** , ~~we may~~ **our business, financial condition and prospects could** be **materially and adversely affected** ~~unable to overcome such rejections~~ . In addition, ~~in the U. S. PTO~~ **our CMOs are responsible for transporting temperature- controlled materials that can be inadvertently degraded during transport due to several factors, rendering certain batches unsuitable for trial use for failure to meet, among others, our integrity** and ~~in comparable agencies in~~ **purity specifications. We and** ~~many~~ **any** ~~foreign jurisdictions,~~ **of our CMOs may also face product seizure or detention or refusal to permit the import or export of products. Our business could be materially adversely affected by business disruptions to our** third **- party providers that could materially adversely affect** ~~parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or~~ **our** ~~cancellation proceedings may be filed against~~ **anticipated timelines, potential future revenue and financial condition and increase our costs and expenses. Each of these risks could delay** ~~our~~ **or** ~~trademarks,~~ **prevent the completion of our preclinical studies** and **clinical trials** ~~our~~ **or** ~~trademarks may not survive such proceedings~~ **the approval of any of our product candidates by the FDA, result in higher costs or adversely impact commercialization of our product candidates** . ~~If we do not secure registrations~~ **See the section titled " Business – Manufacturing "** for **a** ~~our trademarks, we may encounter~~ more ~~difficulty in enforcing~~ **detailed description of our manufacturing plans and assumptions and** ~~them~~ **the factors** ~~against third parties than~~ **that** ~~we otherwise would. Third parties~~ may ~~pursue trademark infringement actions against us~~ **affect the success of our programs. In order to successfully implement our plans and strategies, we will need to grow the size of our organization and we may experience difficulties in managing this growth. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of preclinical and clinical drug development, technical operations, clinical operations, regulatory affairs and** , potentially ~~resulting in substantial costs and material delays. As our activities grow~~ , **sales** ~~we may be subject to an~~ **and marketing. To manage** ~~increasing amount of litigation that is common in the pharmaceutical industry based on allegations of infringement or~~ **our anticipated** ~~other alleged violations of trademarks. Any claims of infringement, with or without merit, could be time consuming, costly, and difficult to defend. Moreover, intellectual property litigation or claims could require us to redesign packaging and advertising materials associated with our packaging, which could result in substantial costs and material delays. Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business Our~~ future **growth** ~~success depends on our ability to retain key executives and to attract~~ , ~~retain~~ **we must**

continue to implement and ~~motivate~~ **improve our managerial, operational and financial personnel and systems, expand our facilities and continue to recruit and train additional** qualified personnel. **Due to our limited financial resources and the limited experience of our management team working together in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel.** We are **highly dependent on our key personnel and anticipate hiring new key personnel. If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy. We are** a ~~clinical~~ **preclinical** ~~-~~-stage biotechnology company with a limited operating history, and, as of December 31, ~~2022~~ **2023** , **we** had ~~69~~ **30** employees. We ~~are~~ **have been and will continue to be** highly dependent on the research and development, clinical and business development expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain " key person " insurance for any of our executives or other employees. ~~Recruiting~~ **Attracting** and retaining qualified ~~scientific, clinical, manufacturing and sales and marketing~~ personnel will also be critical to our success **, including with respect to any strategic transaction that we may pursue** . The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and 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 successfully develop, facilitate regulatory approval of and commercialize product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel 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 rely on consultants and advisors, including scientific and clinical advisors ~~such as our scientific advisory board~~ , to assist us in formulating our discovery and nonclinical and clinical development and commercialization strategy. Our consultants and advisors ~~, including members of our scientific advisory board,~~ may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited. Our **future growth may depend, in part, on our ability to operate in foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties. Our future growth may depend, in part, on our ability to develop and commercialize our product candidates in foreign markets for which we may rely on collaboration with third parties. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the applicable foreign regulatory authority, and may never receive such regulatory approval for any of our product candidates. To obtain separate regulatory approval in many other countries, we must comply with numerous and varying regulatory requirements of such countries regarding safety and efficacy and governing, among other things, clinical trials and commercial sales, pricing and distribution of our product candidates, and we cannot predict success in these jurisdictions. If we fail to comply with the regulatory requirements in international markets and 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 and our business will be adversely affected. Moreover, even if we obtain approval of our product candidates and ultimately commercialize our product candidates in foreign markets, we would be subject to the risks and uncertainties, including the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements and reduced protection of intellectual property rights in some foreign countries. Our estimates of market opportunity and forecasts of market growth may prove to be inaccurate, and even if the markets in which we compete achieve the forecasted growth, our business may not grow at similar rates, or at all. Our market opportunity estimates and growth forecasts are subject to significant uncertainty and are based on assumptions and estimates which may not prove to be accurate. Our estimates and forecasts relating to size and expected growth of our target market may prove to be inaccurate. Even if the markets in which we compete meet our size estimates and growth forecasts, our business may not grow at similar rates, or at all. Our growth is subject to many factors, including our success in implementing our business strategy, which is subject to many risks and uncertainties. Our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. Our** employees **, independent contractors, consultants, commercial collaborators, principal investigators, CROs, CMOs, suppliers and vendors** may engage in misconduct or other improper activities, including ~~non- compliance~~ **noncompliance** with regulatory standards and requirements ~~, which could cause significant liability for us and harm our reputation~~ . We are exposed to the risk ~~of~~ **that our** ~~employee~~ **employees** ~~fraud~~ **, independent contractors, consultants, commercial collaborators, principal investigators, CROs, CMOs, suppliers and vendors acting for or on our behalf may engage in misconduct** or other **improper activities** ~~misconduct, including intentional failures to (i) comply with FDA regulations or similar regulations of comparable non- U~~ . **We** ~~S. regulatory authorities, (ii) provide accurate information to the FDA or comparable non- U. S. regulatory authorities, (iii) comply with manufacturing standards we~~ have **adopted a code of** ~~established, (iv) comply with the Foreign Corrupt Practices Act and 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, or (v) report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct~~ --- **conduct** ~~could also involve the improper use of information obtained in~~

~~the course of clinical trials, which could result in regulatory sanctions~~ and **ethics, but it** ~~serious harm to our reputation. It~~ is not always possible to identify and deter ~~employee~~ misconduct ~~,~~ **by these parties** and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to ~~be~~ **comply with these laws or regulations. Our internal information technology systems, or those of any of our CROs, manufacturers, other contractors or consultants, third party service providers, or potential future collaborators, may fail or suffer security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data, employee data or personal data, which could result** in ~~compliance~~ **additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations. In the ordinary course of our business, we and the third parties upon which we rely collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, process) proprietary, confidential, and sensitive data, including personal data, intellectual property, trade secrets, and other sensitive data (collectively, sensitive information). Despite the implementation of security measures in an effort to protect systems that store our information, given their size and complexity and the increasing amounts of information maintained on our internal information technology systems and those of our third- party CROs, other contractors (including sites performing our clinical trials), third party service providers and supply chain companies, and consultants, these systems are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners and / or other third parties, or from cyber- attacks by malicious third parties, which may compromise our system infrastructure or lead to the loss, destruction, alteration or dissemination of, or damage to, our data. Some actors now engage and are expected to continue to engage in cyber- attacks, including without limitation nation- state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we, and the third parties upon which we rely, may be vulnerable to a heightened risk of these attacks, including retaliatory cyber- attacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, ability to provide our products or services, loss of sensitive data and income, reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments. To the extent that any disruption or security breach were to result in loss, destruction, unavailability, alteration or dissemination of, or damage to, our data or applications, or for it to be believed or reported that any of these occurred, we could incur liability and reputational damage and the development and commercialization of our product candidates could be delayed. Further, our insurance policies may not be adequate to compensate us for the potential losses arising from any such disruption in, or failure or security breach of, our systems or third- party systems where information important to our business operations or commercial development is stored. Our fully- remote workforce may create additional risks for our information technology systems and data because our employees work remotely and utilize network connections, computers, and devices working at home, while in transit and in public locations. Additionally, business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. We may be unable in the future to detect vulnerabilities in our information technology systems because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after a security incident has occurred. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities. Applicable data privacy and security obligations may require us to notify relevant stakeholders of security incidents. Such disclosures are costly, and the disclosure or the failure to comply** with such ~~laws~~ **requirements could lead to adverse consequences. We rely on third- party service providers and technologies to operate critical business systems to process sensitive information in a variety of contexts. Our ability to monitor these third parties' information security practices is limited** ~~, standards or regulations~~ **and these third parties may not have adequate information security measures in place** . If **our third- party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third- party service providers fail to satisfy their privacy or security- related obligations to us,** any **award may be insufficient to cover our damages, or we may be unable to recover** such **award. In addition** ~~actions are instituted against us~~ , **supply- chain attacks have increased in frequency** and **severity, and** we ~~are~~ **cannot guarantee that third parties' infrastructure in our supply chain or our third- party partners' supply chains have** not **been compromised** ~~successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions~~ . If ~~product liability lawsuits are brought against us,~~ we **(** ~~may incur substantial liabilities and may be required to limit commercialization of our~~ - **or** ~~product candidates. We face an inherent risk of product liability as~~ a **third party upon whom** ~~result of testing our product candidates in clinical trials and will face an even greater risk if~~ we **rely) experience a security incident** ~~commercialize any products. For example, we may be sued if our product candidates cause~~ or are perceived to **have experienced a security incident, we may experience adverse consequences, such as government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and / or oversight; restrictions on processing sensitive information (including personal data); litigation**

(including class claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant consequences may cause ~~injury~~ **stakeholders (including investors and potential customers) to stop supporting** ~~or~~ **our platform, deter new customers from products, and negatively impact our ability to grow and operate our business. Our contracts may not contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts** are ~~found~~ **sufficient** to **protect us from liabilities** ~~be otherwise unsuitable during clinical trials~~ , ~~manufacturing~~ **damages** , ~~marketing~~ **or claims related to** ~~or~~ **our** ~~sale~~ **data privacy and security obligations** . ~~Any~~ **We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, that** such ~~product liability~~ **coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future** claims ~~may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability 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, liability claims may result in: • inability to bring a product candidate to the market; • decreased demand for our products; • injury to our reputation; • withdrawal of clinical trial participants and inability to continue clinical trials; • initiation of investigations by regulators; • costs to defend the related litigation; • diversion of management' s time and our resources; • substantial monetary awards to trial participants or patients; • product recalls, withdrawals or labeling, marketing or promotional restrictions; • loss of revenue; • exhaustion of any available insurance and our capital resources; • the inability to commercialize any product candidate; and • decline in our share price. Our product liability insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise. Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited~~ . Under Section 382 of the Internal Revenue Code of 1986, as amended **(" the Code")** , if a corporation undergoes an " ownership change, " generally defined as a greater than 50 % change (by value) in its equity ownership over a three- year period, the corporation' s ability to use its pre- change net operating loss carryforwards, or NOLs, and other pre- change tax attributes (such as research tax credits) to offset its post- change income or taxes may be limited. ~~It~~ **Upon certain events since our conversion from a Delaware limited liability company to a Delaware corporation in 2015, it** is possible that we may have triggered an " ownership change " limitation. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership (some of which are outside of our control). As a result, if we earn net taxable income, our ability to use our pre- change NOLs and other pre- change tax attributes to offset U. S. federal taxable income or taxes may be subject to limitations, which could potentially result in increased future tax liability to us. Our NOLs and other tax attributes arising before our conversion from a Delaware limited liability company to a Delaware corporation in 2015 also may be limited by the Separate Return Limitation Year rule, which could increase our U. S. federal tax liability. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. ~~Risks~~ **We are subject to stringent and changing laws, regulations and standards, and contractual obligations relating to privacy, data protection, and data security. The actual or perceived failure to comply with such obligations could lead to government enforcement actions (which could include civil or criminal penalties), fines and sanctions, private litigation and / or adverse publicity and could negatively affect our operating results and business. We, and third parties who we work with are or may become subject to numerous domestic and foreign laws, regulations, and standards relating to privacy, data protection, and data security, the scope of which is changing, subject to differing applications and interpretations, and may be inconsistent among countries, or conflict with other rules. We are or may become subject to the terms of contractual obligations** ~~Related~~ **related** to **privacy, data protection and data security.** Our **obligations** ~~Common Stock Our executive officers, directors and principal stockholders, if they choose to act together,~~ may **also change** ~~continue to have the ability to control all matters submitted to stockholders for~~ - **or** ~~approval~~ **expand as our business grows** . **The actual** ~~We have a concentrated stockholder base and our~~ - **or** ~~executive officers and directors, combined~~ **perceived failure by us or third parties related to us to comply** with **such laws** ~~our stockholders who~~ , ~~to~~ **regulations and obligations could increase** our ~~knowledge~~ **compliance and operational costs** , **expose us to regulatory scrutiny** ~~each owned more than 5 % of our outstanding common stock~~ , **actions** ~~in the aggregate~~ , **fines and penalties** ~~beneficially own shares representing a substantial number of our capital stock as of December 31~~ , ~~2022. As a~~ result ~~, if these stockholders were to choose to act together, they may be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would likely control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may: • delay, defer or prevent a change~~ in **reputational harm** ~~control; • entrench our management and the board of directors; or • impede a merger~~ , ~~consolidation~~ **lead to a loss of customers** , ~~takeover or other business combination involving us that other stockholders may desire or may~~ result in **litigation** ~~you obtaining a premium for your shares. Failure to achieve~~ and **liability, and otherwise cause** ~~maintain effective internal control over financial reporting in accordance with Section 404 of the Sarbanes- Oxley Act could have~~ a material adverse effect on our business **, financial condition** and **results of operations. See the section titled " Business – Government Regulation – Data Privacy and Security " for a more detailed description of the laws that may affect our ability to operate. If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse**

effect on the success of our business. We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations may involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. We may be subject to adverse legislative or regulatory tax changes that could negatively impact our financial condition. The rules dealing with U. S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U. S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect our stockholders or us. We assess the impact of various tax reform proposals and modifications to existing tax treaties in all jurisdictions where we have operations to determine the potential effect on our business and any assumptions we have made about our future taxable income. We cannot predict whether any specific proposals will be enacted, the terms of any such proposals or what effect, if any, such proposals would have on our business if they were to be enacted. For example, the United States recently enacted the Inflation Reduction Act of 2022, which implements, among other changes, a 1 % excise tax on certain stock ~~price~~ **buybacks. In addition, beginning in 2022, the Tax Cuts and Jobs Act eliminated the previously available option to deduct research and development expenditures and requires taxpayers to amortize them generally over five years for research activities conducted in the United States and over 15 years for research activities conducted outside the United States. The U. S. Congress is considering legislation that would restore the current deductibility of research and development expenditures; however, we have no assurance that the provision will be repealed or otherwise modified. Such changes, among others, may adversely affect our effective tax rate, results of operation and general business condition. We may acquire businesses or products, or form strategic alliances, in the future, and may not realize the benefits of such acquisitions. 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 product candidates or products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. There is no assurance that, following any such acquisition, we will achieve the synergies expected in order to justify the transaction, which could result in a material adverse effect on our business and prospects. We maintain our cash at financial institutions, often in balances that exceed federally- insured limits. The failure of financial institutions could adversely affect our ability to pay our operational expenses or make other payments. Our cash held in non- interest- bearing and interest- bearing accounts exceeds the Federal Deposit Insurance Corporation (" FDIC") insurance limits. If such banking institutions were to fail, we could lose all or a portion of those amounts held in excess of such insurance limitations. For example, the FDIC took control of Silicon Valley Bank on March 10, 2023. The Federal Reserve subsequently announced that account holders would be made whole. However, the FDIC may not make all account holders whole in the event of future bank failures. In addition, even if account holders are ultimately made whole with respect to a future bank failure, account holders' access to their accounts and assets held in their accounts may be substantially delayed. Any material loss that we may experience in the future or inability for a material time period to access our cash and cash equivalents could have an adverse effect on our ability to pay our operational expenses or make other payments, which could adversely affect our business** . Pursuant to ~~Section 404 of~~ the **terms** ~~Sarbanes- Oxley Act~~ of **the December** ~~2002~~ - **2023 SPA** ~~, or the Sarbanes- Oxley Act~~ , we are required to **recommend that** ~~furnish a report by our management on our internal control over financial reporting. However, while we remain a non- accelerated filer, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles in the United States. We may encounter problems or~~ **our stockholders approve** ~~delays in implementing any changes necessary to make a favorable assessment of our internal control over financial reporting. If we cannot favorably assess~~ the ~~effectiveness~~ **conversion** of **all outstanding shares of** ~~our internal control over financial reporting, or~~ **our Series B Preferred Stock into shares** ~~if our independent registered public accounting firm is unable to provide an unqualified attestation report on our internal controls when required, investors could lose confidence in our financial information and the price~~ of our common stock **. We cannot guarantee that our stockholders will approve this matter, and if they fail to do so, we may be required to settle such shares in cash and our operations may be materially harmed. Under the terms of the December 2023 SPA, we agreed to use best efforts to obtain the requisite approval for the conversion of all outstanding shares of Series B Preferred Stock issued in the December 2023 PIPE into shares of our common stock, as required by the Nasdaq listing rules, at our 2024 annual meeting of stockholders and, if such approval is not obtained at that meeting, to seek to obtain such approval at a stockholders meeting to be held at least every 90 days thereafter until such approval is obtained, which** ~~could~~ **would** ~~decline~~ **be time consuming and costly** . Additionally, **if** ~~the existence of any material weakness or~~ **our stockholders do** ~~significant deficiency would require management to devote significant time and incur significant expense to remediate any such material weaknesses or significant deficiencies and management may~~ not ~~be able to remediate any such material weaknesses or significant deficiencies in a~~ timely **approve the conversion** ~~manner. The existence~~ of ~~any material weakness in~~ our **Series B Preferred Stock, then the holders of** ~~internal control over financial reporting could also result in errors in~~ our ~~financial statements that could~~ **Series B Preferred Stock may**

be entitled to require us to ~~restate our financial statements causing us~~ **settle their shares of Series B Preferred Stock for cash at a price per share equal** to **the** ~~fail~~ **fair value** ~~to meet our reporting obligations and cause stockholders to lose confidence in our reported financial information, all~~ of ~~which~~ **the Series B Preferred Stock at such time, as described in our Series B Certificate of Designation relating to the Series B Preferred Stock. If we are forced to settle a significant amount of the Series B Preferred Stock, it** could materially ~~and adversely~~ affect ~~us~~ **our results of operations** . **Anti- takeover** ~~Provisions~~ **provisions** in our ~~corporate~~ charter documents and under Delaware law **and the terms of some of our contracts** could make an acquisition of **us** ~~our company, which may be beneficial to our stockholders,~~ more difficult and may prevent attempts by our stockholders to replace or remove our ~~current~~ management. Provisions in our ~~certificate~~ **Certificate** of ~~incorporation~~ **Incorporation** and ~~our bylaws~~ **Bylaws** may ~~discourage,~~ delay or prevent **an** ~~a merger,~~ acquisition or ~~other~~ **a** change in **management** ~~control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares~~ . These provisions **include a prohibition on actions by written consent** ~~could also limit the price that investors might be willing to pay in the future for shares~~ of our ~~common~~ **stockholders and the ability of our board of directors to issue Preferred** ~~stock~~ **Stock without stockholder approval** ~~, thereby depressing the market price of our common stock~~ . In addition, because **we are incorporated in Delaware, we are governed by the provisions of Section 203 of the DGCL, which prohibits stockholders owning in excess of 15 % of our outstanding voting stock from merging or combining with us. Although we believe these provisions collectively will provide for an opportunity to receive higher bids by requiring potential acquirers to negotiate with** our board of directors **,** ~~is responsible for appointing the~~ **they** ~~members of our management team~~ **would apply even if the offer may be considered beneficial by some stockholders. In addition** , these provisions may frustrate or prevent any attempts by our stockholders to replace or remove ~~our~~ **then** current management by making it more difficult for stockholders to replace members of ~~our~~ **the** board of directors ~~. Among other things~~ , **which** ~~these provisions: • establish a classified board of directors such that only one of three classes of directors~~ is **responsible** ~~elected each year; • allow the authorized number of our directors to be changed only by resolution of our board of directors; • limit the manner in which stockholders can remove directors from our board of directors; • establish advance notice requirements~~ for **appointing the members** ~~stockholder proposals that can be acted on at stockholder meetings and nominations to our board~~ of **management. In addition, the Series A Certificate** ~~directors; • require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent; • limit who may call stockholder meetings; • authorize our board~~ of ~~directors~~ **Designation relating** to ~~issue~~ **our Series A** ~~preferred~~ **Preferred** ~~stock~~ **Stock may delay or** ~~without stockholder approval, which could be used to institute a " poison pill " that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing~~ --- **prevent a change in control** ~~acquisitions that have not been approved by our board~~ of **our company. At any time while** ~~directors; and • require the approval of the holders of~~ at least **30 % of the originally issued Series A Preferred Stock remains issued and outstanding, we may not consummate a Fundamental Transaction (as defined in the Series Certificate of Designation) or any merger or consolidation of the Company with or into another entity or any stock sale** ~~two~~ - **to, or** ~~- thirds of the~~ **other business combination in which our stockholders immediately before such transaction do not hold at least a majority of our capital stock immediately after such transaction, without the affirmative** ~~votes~~ - **vote of the holders of a majority of the then outstanding shares of the Series A Preferred Stock. This provision of the Series A Certificate of Designation may make it more difficult for us to enter into any of the aforementioned transactions. Our Certificate of Incorporation and Bylaws provide** that ~~all~~ **the** ~~our~~ **Court** ~~stockholders would be entitled to cast to amend or repeal specified provisions~~ of **Chancery** ~~our certificate~~ of ~~incorporation or bylaws. Moreover, we are governed by~~ the ~~provisions~~ **State** of ~~Section 203 of the~~ Delaware ~~General Corporation Law, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination~~ is ~~approved in a prescribed manner. Any of these~~ -- **the** ~~provisions of our charter documents or Delaware law could, under certain circumstances, depress the market price of our common stock. Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware as the sole and~~ exclusive forum ~~for~~ certain types of actions and proceedings that may be initiated by our stockholders, and our ~~amended and restated bylaws~~ **Bylaws** ~~designates~~ - **designate** the federal courts of the United States as the exclusive forum for actions arising under the Securities Act, each of which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or agents. Our ~~amended and restated certificate~~ **Certificate** of ~~incorporation~~ **Incorporation and Bylaws** ~~provides~~ - **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 derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to us or our stockholders, any action asserting a claim arising pursuant to any provision of the DGCL, our ~~amended and restated certificate~~ **Certificate** of ~~incorporation~~ **Incorporation** ~~or our~~ - **or our** ~~amended and restated bylaws~~ **Bylaws** or 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 and the claim not being one which is vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery or for which the Court of Chancery does not have subject matter jurisdiction. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our ~~amended and restated certificate~~ **Certificate** of ~~incorporation~~ **Incorporation and Bylaws** . Our ~~restated bylaws~~ **Bylaws** provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (a **"** Federal Forum Provision **"**). Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware

Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court. **In addition, investors cannot waive compliance with the federal securities laws and the rules and regulations thereunder. These choice of forum provisions will not apply to claims brought to enforce a duty or liability created by the Exchange Act.** These choice of forum provisions may limit our stockholders' ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, employees or agents, which may discourage such lawsuits against us and our directors, officers, employees and agents even though an action, if successful, might benefit our stockholders. Stockholders who do bring a claim in the specified courts could face additional litigation costs in pursuing any such claim. The specified courts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments or results may be more favorable to us than to our stockholders. Alternatively, if a court were to find these provisions of our governance documents inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have a material adverse effect on our business, financial condition or results of operations. **We do not anticipate that we will pay any cash dividends in the foreseeable future.** The **current expectation is that we will retain our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain, if any, for the foreseeable future. On December 7, 2023, we entered into a registration rights agreement (the " December 2023 RRA ") with the December 2023 Investors. Pursuant to the December 2023 RRA, we agreed to file a resale registration statement to register the Registrable Securities (as defined in the December 2023 RRA) (the" Registration Statement"). The registration statement was filed on December 22, 2023 in order to satisfy our obligations under the December 2023 RRA. We have agreed to use our commercially reasonable efforts to cause the Registration Statement to be declared effective by the SEC as soon as practicable. If, following receipt of stockholder approval of the conversion of all issued and outstanding Series B Preferred Stock into shares of common stock in accordance with the Nasdaq Stock Market Rules (the " Series B Conversion Proposal"), the Registration Statement is not declared effective prior to, subject to certain limited exceptions pursuant to the December 2023 RRA, the 90th calendar day following the closing date of the December 2023 PIPE (or, in the event the SEC reviews and has written comments to the Registration Statement, the 120th calendar day following such closing date), among other events (each event, a " Registration Failure "), then we will be required to make pro rata payments to each Investor of the then outstanding Registrable Securities in an amount equal to one percent of the aggregate amount invested by such December 2023 Investor for the Registrable Securities then held by such December 2023 Investor for the initial day of a Registration Failure and for each 30 day period thereafter until the Registration Failure is cured. If the Registration Statement is declared effective, the shares subject to the Registration Statement will no longer constitute restricted securities and may be sold freely in the public markets, subject to lapse on any related contractual restrictions related thereto of any December 2023 Investor and, for shares of common stock issuable upon the conversion of Series B Preferred Stock, the approval of our stockholders of such conversion. If our stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market after legal restrictions on resale lapse, the trading price of our common stock could decline. In addition, shares of our common stock that are subject to our outstanding options will become eligible for sale in the public market to the extent permitted by the provisions of various vesting agreements and Rules 144 and 701 under the Securities Act. We expect that we will need significant additional capital to fund our current and future operations, including to complete potential clinical trials for our product candidates. To raise capital, 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. As a result, our stockholders may experience additional dilution, which could cause our stock price to fall. Pursuant to our equity incentive plans, we may grant equity awards and issue additional shares of our common stock to our employees, directors and consultants, and the number of shares of our common stock reserved for future issuance under certain of these plans will be subject to automatic annual increases in accordance with the terms of the plans. To the extent that new options are granted and exercised, or we issue additional shares of common stock in the future, our stockholders may experience additional dilution, which could cause our stock price to fall. Our principal stockholders own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval. Our directors, officers, 5 % stockholders, and their affiliates currently beneficially own a substantial portion of our outstanding voting stock. Therefore, these stockholders have the ability and may continue to have the ability to influence us through this ownership position. These stockholders may be able to determine some or all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders. The market price of our common stock has historically been volatile, and the market price of our common stock may decline in the future. The market** price of our common stock has been **,** and may **continue to** be **, subject to significant fluctuations. Market prices for securities of early- stage pharmaceutical, biotechnology, and other life sciences companies have historically been particularly** volatile **. Some of the factors that may cause the market price** ~~and fluctuate substantially, which could result in substantial losses for purchasers~~ of our common stock ~~. Our~~ **to fluctuate include: • our ability to obtain regulatory approvals for our product candidates, and delays or failures to obtain such approvals; • failure of any of our product candidates, if approved, to achieve commercial success; • failure to maintain our existing third- party license and supply agreements; • changes in laws or regulations applicable to our product candidates; • any inability to obtain adequate**

supply of our product candidates or the inability to do so at acceptable prices; • adverse regulatory authority decisions; • introduction of new products, services, or technologies by our competitors; • failure to meet or exceed financial and development projections we may provide to the public and the investment community; • the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community; • announcements of significant acquisitions, strategic collaborations, joint ventures, or capital commitments by us or our competitors; • disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies; • additions or departures of key personnel; • significant lawsuits, including patent or stockholder litigation; • if securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our business and stock ~~price is volatile~~ **; • changes in the market valuations of similar companies; • general market or macroeconomic conditions, including global inflationary pressures, rising interest rates, general economic slowdown or a recession, changes in monetary policy, instability in financial institutions and the prospect of a shutdown of the U** . ~~The~~ **S. federal government; • geopolitical instability, including the ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China; • sales of our common** stock **by us or our stockholders in the future; • trading volume of our common stock; • announcements by commercial partners or competitors of new commercial products, clinical progress or the lack thereof, significant contracts, commercial relationships, or capital commitments; • the introduction of technological innovations or new therapies that compete with our potential products; • changes in the structure of health care payment systems; and • period- to- period fluctuations in our financial results. Moreover, the capital** ~~market~~ **markets** in general ~~and the market for smaller biotechnology companies in particular~~ have experienced ~~extreme~~ **substantial** volatility that has often been unrelated to the operating performance of ~~particular~~ **individual** companies. ~~The~~ **These broad market fluctuations may also adversely affect the trading price of our common stock. In the past, following periods of volatility in the** market price ~~for our common stock may be influenced by many factors, including: • the success or failure~~ of **a company' s securities, stockholders have often instituted class action securities litigation against** ~~competitive products or technologies; • results of ongoing or planned clinical trials of our product candidates or~~ those ~~of our competitors; • regulatory or legal developments in the United States and other countries; • developments or disputes concerning patent applications, issued patents or other proprietary rights; • the recruitment or departure of key personnel; • the level of expenses related to any of our product candidates or clinical development programs; • the results of our efforts to discover, develop, acquire or in- license additional product candidates or products; • actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts; • operating results that fail to meet expectations of securities analysts that cover our company; • variations in our financial results or those of~~ companies ~~that are perceived to be similar to us; • changes in the structure of healthcare payment systems; • market conditions in the pharmaceutical and biotechnology sectors; • general economic and market conditions including rising interest rates and inflation, as well as the possibility of a recession or further economic downturn, and the economic impact of the war in Ukraine and its potential supplier chain impacts and the ongoing COVID- 19 pandemic; and • the other factors described in this " Risk Factors " section~~ . **Such litigation** ~~We have broad discretion in the use of the net proceeds from our public and private offerings and may not use them effectively. Our management has broad discretion in the application of the net proceeds from our public and private offerings~~ , **if instituted,** ~~and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Our management could spend the net proceeds from our public and private offerings 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~~ **substantial costs and diversion of management attention and resources, which** 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 their use, we may invest the net proceeds from our public and private offerings in a manner that does not produce income or that loses value. Future sales of our common stock in the public market could cause the market price of our common stock to drop~~ significantly **harm** ~~, even if our business is doing well. Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock and make it more difficult for you to sell your~~ - **our profitability** ~~common stock at a time~~ and **reputation** ~~price that you deem appropriate~~ . **We incur costs** ~~Moreover, we have also registered under the Securities Act shares of common stock that we may issue under our equity compensation plans. In July 2020, we filed a new shelf registration statement on Form S- 3 that was declared effective in July 2020 by the SEC for the potential offering, issuance~~ and **demands upon management** ~~sale by us of up to $ 400. 0 million of our common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock and debt securities, subscription rights to purchase common stock and units consisting of all or some of these securities; however, for so long~~ as **a result** ~~the aggregate market value~~ of **complying** ~~our common equity held by our non- affiliates, or public float, is less than $ 75 million, we will only be able to sell securities~~ with ~~an aggregate market value of up to one- third of our public float. If we sell common stock, preferred stock, convertible securities and other equity securities in other transactions pursuant to our shelf registration statements on Form S- 3, existing investors may be materially diluted by such subsequent sales and new investors could gain rights superior to our existing stockholders. In May 2021, we filed a shelf registration statement on Form S- 3, that was declared effective on June 8, 2021 by the SEC, registering up to 19, 020, 434 shares of our common stock held by 667, L. P., or 667, and Baker Brothers Life Sciences, L. P., or Life Sciences, and together with 667, the Baker Funds, which includes 15, 610, 328 shares of common stock issuable upon the exercise of pre- funded warrants held by the Baker Funds, for resale or other disposition from time to time as described in the registration statement. In May 2022, we entered into an " at- the- market " offering of our common stock pursuant to a sales agreement between us and JonesTrading Institutional Services LLC, or JonesTrading, under a shelf registration statement on Form S- 3. Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to~~

~~JonesTrading at any time throughout the term of the sales agreement, which has a term equal to the term of the registration statement on Form S- 3 unless otherwise terminated earlier by us or JonesTrading pursuant to the terms of the sales agreement. The number of shares that are sold by JonesTrading after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with JonesTrading. Because the price per share of each share sold pursuant to the sales agreement will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued. Issuances of any shares sold pursuant to the sales agreement will have a dilutive effect on our existing stockholders. In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise, including upon exercise of our pre- funded warrants. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline. We will not receive a significant amount, or potentially any, additional funds upon the exercise of our pre- funded warrants; however, any exercise would increase the number of shares eligible for future resale in the public market and result in substantial dilution to our stockholders. As of December 31, 2022, we have issued pre- funded warrants to purchase a total of 34, 982, 640 shares of our common stock, of which 6, 091, 062 have been exercised and 28, 891, 578 are currently outstanding. Each pre- funded warrant is exercisable for $ 0. 0001 per share of common stock underlying such pre- funded warrant, 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 will result in substantial dilution to the then~~ - **the laws** ~~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. There is no public market for our pre- funded warrants. There is no public trading market for our pre- funded warrants issued in the February 2019, April 2020 and May 2022 public offerings, and we do not expect a market to develop. In addition, we do not intend to apply to list the pre- funded warrants on any securities exchange or nationally recognized trading system, including the Nasdaq Global Market. Without an~~ **and regulations regulating** ~~active market, the liquidity of the pre- funded warrants will be limited and their value may be adversely impacted. Additionally, each holder of pre- funded warrants will not be entitled to exercise any portion of any pre- funded warrant, which, upon giving effect to such exercise, would cause (i) the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4. 99 %, or 9. 99 % for certain holders, of the number of shares of our common stock outstanding immediately after giving effect to the exercise, or (ii) the combined voting power of our securities beneficially owned by the holder (together with its affiliates) to exceed 4. 99 %, or 9. 99 % for certain holders, of the combined voting power of all of our securities then outstanding immediately after giving effect to the exercise. However, any holder may increase or decrease such percentage to any other percentage (not in excess of 19. 99 % for the majority of such warrants) upon at least 61 days' prior notice from the holder to us. We are a " smaller reporting company, " and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors. We are a " smaller reporting company " under the Exchange Act. For so long as we remain a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other~~ public companies ~~that are not smaller~~ **. We incur significant legal, accounting, and other expenses associated with public company** reporting ~~companies~~ **requirements** . **We also incur costs associated** ~~These exemptions include: • being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements,~~ with **corporate governance** ~~correspondingly reduced " Management' s Discussion and Analysis of Financial Condition and Results of Operations " disclosure; • not being required to comply with the auditor attestation~~ requirements **, including requirements under** ~~in the assessment of our internal control over financial reporting of Section 404 (b) of~~ the Sarbanes- Oxley Act **, as** ~~; and • reduced disclosure obligations regarding executive compensation. We may continue to take advantage of these exemptions until we are no longer a smaller reporting company. We will~~ **well as rules implemented** ~~remain a smaller reporting company if we have either (i) less than $ 250 million in market value of our shares held~~ by ~~non- affiliates as of the last business day of our second fiscal quarter or (ii) less than $ 100 million of annual revenues in our most recent fiscal year and a market value of our shares held by non- affiliates less than $ 700 million as of the last business day of our second fiscal quarter. We may choose to take advantage of some but not all of these~~ -- **the SEC** ~~scaled disclosure requirements. Therefore, the information that we provide stockholders may be different than one might get from other public companies. Further, if some investors find our shares of common stock less attractive as a result, there may be a less active trading market for our shares of common stock and the market price of such shares of common stock may be more volatile. We will continue to incur 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 and corporate governance practices. As a public company, and particularly now that we are no longer an~~ **and** ~~emerging growth company, we incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes- Oxley Act, the Dodd- Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The~~ Nasdaq **. These** ~~Global Market and other applicable securities~~ rules and regulations ~~impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will continue to~~ increase our legal and financial compliance costs and ~~will~~ make some activities more time- consuming and costly. ~~For example, we expect that these~~ **These** rules and regulations may **also** make it ~~more~~ difficult and ~~more~~ expensive for us to obtain ~~and maintain director~~ **directors '** and ~~officer~~ **officers '** liability insurance **. As a result** , ~~which in turn could make~~ it **may be** more difficult for us to attract and retain

qualified ~~members of~~ **individuals to serve on** our board of directors **or as our executive officers, which may adversely affect investor confidence and could cause our business or stock price to suffer. If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business, or our market, our stock price and trading volume could decline. The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. Equity research analysts may elect not to provide research coverage of our common stock and such lack of research coverage may adversely affect the market price of our common stock. In the event we do have equity research analyst coverage, we will not have any control over the analysts or the content and opinions included in their reports. The price of our common stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of us or fails to publish reports on us regularly, demand for our common stock could decrease, which in turn could cause our stock price or trading volume to decline. If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our common stock may be negatively affected** . We are ~~evaluating~~ **subject to** ~~these~~ -- **the reporting requirements of the Exchange Act, the Sarbanes- Oxley Act, and the** rules and regulations ~~, and cannot predict or estimate the amount~~ of **Nasdaq** ~~additional costs we may incur or the timing of such costs~~ . ~~These~~ -- **The Sarbanes- Oxley Act requires** ~~rules and regulations are often subject to varying interpretations~~ , **among** ~~in many cases due to their~~ - **other things** ~~lack of specificity~~ , **that we maintain effective** ~~and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to~~ disclosure **controls** and **procedures and** ~~governance practices. Pursuant to Section 404, we are required to furnish a report by our management on our~~ internal control over financial reporting. **We must perform system** ~~As discussed above, if we cease to be a non- accelerated filer, we will be required to include an~~ **and** ~~attestation report on~~ **process evaluation and testing of our** internal control over financial reporting ~~issued~~ **to allow management to report on the effectiveness of our internal controls over financial reporting in our annual report filing for that year, as required by Section 404 of the Sarbanes- Oxley Act. This requires that we incur substantial professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts. We may experience difficulty in meeting these reporting requirements in a timely manner for each period. We may or any subsequent testing** by our independent registered public accounting firm **may discover weaknesses** ~~as required by Section 404 (b). To achieve compliance with Section 404 within the prescribed period, we will be engaged~~ in ~~a process to document and evaluate~~ our **system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our** internal control over financial reporting ~~, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we~~ will not **prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system' s objectives will** be **met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected. If we are not** able to **comply** ~~conclude, within~~ -- **with** the **requirements of** ~~prescribed timeframe or at all, that our internal control over financial reporting is effective as required by~~ Section 404 ~~. If we identify one~~ **of the Sarbanes- Oxley Act,** or ~~more material weaknesses~~ **if we are unable to maintain proper and effective internal controls** , it could result in ~~an adverse reaction in the financial markets due to~~ a ~~loss~~ **material misstatement** of ~~confidence in the reliability of~~ our ~~consolidated~~ financial statements **that would** ~~. Since we do~~ not **be prevented or detected** ~~anticipate paying any cash dividends~~ on **a timely basis, which could require a restatement, cause us to be subject to sanctions** ~~our~~ - **or** ~~capital stock in~~ **investigations by Nasdaq, the SEC, or** ~~the~~ **other** ~~foreseeable future~~ **regulatory authorities** , **cause investors to lose confidence in our financial information, or cause our** stock price ~~appreciation~~ **to decline. As a public company** , ~~if any~~ **we incur significant legal** , **accounting, insurance, and other expenses, and our management and other personnel have and** will **need** ~~be your sole source of gain. We have never declared or paid cash dividends on our capital stock. We currently intend~~ to ~~retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, appreciation, if any, in the market price of our common stock will be your sole source of gain for the foreseeable future. The price of our common stock may not meet the requirements for continued~~ - **continue** ~~listing on Nasdaq. If we fail~~ to ~~regain~~ **devote a substantial amount of time to** compliance **initiatives** ~~with the minimum listing requirements, our common stock will be subject to delisting. Our ability to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if our common stock is delisted. The continued listing standards of Nasdaq require, among other things, that the minimum bid price of a listed company' s stock be at or above $ 1. 00. If the closing minimum bid price is below $ 1. 00 for a period of more than 30 consecutive trading days, the listed company will fail to be in compliance with Nasdaq' s listing rules and, if it does not regain compliance within the grace period, will be subject to delisting. As previously reported on January 18, 2023, we received a notice from the Nasdaq Listing Qualifications Department notifying us that for 30 consecutive trading days, the bid price of our common stock had closed below the minimum $ 1. 00 per share requirement. In accordance with Nasdaq' s listing rules, we were afforded a grace period of 180 calendar days, or until July 12, 2023, to regain compliance with the bid price requirement. In order to regain compliance, the bid price of our common stock must close at a price of at least $ 1. 00 per share for a minimum of 10 consecutive trading days. If we fail to regain compliance~~

by July 12, 2023, we may be eligible for a second 180 day compliance period if we elect to transfer to The Nasdaq Capital market, provided that, on such date, we meet the continued listing requirement for market value of publicly held shares and all other applicable Nasdaq listing requirements (other than the minimum closing bid price requirement) and we provide written notice to Nasdaq of our intention to cure the deficiency during the second compliance period, by effecting a reverse stock split, if necessary. Such extension of the grace period would be subject to Nasdaq' s discretion, and there can be no guarantee that we would be granted an extension. We cannot provide any guarantee that we will regain compliance during the grace period or be able to maintain compliance with Nasdaq' s listing requirements in the future. If we are not able to regain compliance during the grace period, or any extension of the grace period for which we may be eligible, our common stock will be subject to delisting and" penny stock" rules. Delisting from Nasdaq could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities. General Risk Factors 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. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. Although we maintain workers' compensation insurance that we believe is consistent with industry norms to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, we cannot assure you that it will be sufficient to cover our liability in such cases. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our discovery, nonclinical and clinical development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. Our information technology systems, or those used by our CROs, third- party vendors, contractors or consultants, may fail or suffer security breaches, cyber- attacks, and loss of data, which could harm our business, reputation, financial condition, and operations **operating** . Cyber- attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Despite the implementation of security measures, our information technology systems and those of our strategic partners and third parties on whom we rely are vulnerable to cyber- attacks, security breaches, damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber- attacks could include the deployment of harmful malware, ransomware, denial- of- service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber- attacks also could include phishing attempts or e- mail fraud to cause payments or information to be transmitted to an unintended recipient. Furthermore, we have little or no control over the security measures and computer systems of third parties including any CROs we may work with in the future. While we and, to our knowledge, our third- party strategic partners have not experienced any such material system failure, accident or security breach to date, if such an event were to occur, it could result in material negative consequences for us including interruptions in our operations, the operations of our strategic partners, or our manufacturers or suppliers, misappropriation of confidential business information and trade secrets, disclosure of corporate strategic plans, and result in material disruptions of our product candidate development programs. Additionally, the costs to us or our CROs, third- party vendors, or other contractors or consultants we may utilize to mitigate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures designed to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected system failures, interruptions, delays, cessation of service and other harm to our business and our competitive position. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts, and we may incur substantial costs to attempt to recover or reproduce the data. If any disruption or security breach resulted in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, including personal information or health information, we could incur liability, or the further development of our product candidates could be delayed. Moreover, if a security breach affects our systems or results in the unauthorized access, use or disclosure of personal information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media and / or affected individuals pursuant to various federal, state and international privacy and security laws, if applicable, including HIPAA or HITECH and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a **public** risk of loss or litigation and potential liability under laws, regulations and contracts that protect the privacy and security of personal information. For example, the California Consumer Privacy Act, or the CCPA, imposes a private right of action for security breaches that could lead to some form of remedy including regulatory scrutiny, fines, private right of action settlements, and other consequences. Additional states, including Virginia, Connecticut, Colorado, and Utah, have recently enacted privacy- related laws, and legislation is pending in many other states. The financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we may maintain, and there can be no assurance that the limitations of

liability in any of our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above. Any of the foregoing could have a material adverse effect on our business, reputation, results of operations, financial condition and prospects. We depend on our information technology and infrastructure, and disruptions could compromise sensitive information related to our business or other personal information or prevent us from accessing critical information, which could adversely affect our business, reputation, results of operations, financial condition and prospects. We rely on the efficient and uninterrupted operation of information technology systems to manage our operations, to process, transmit, and store electronic and financial information, and to comply with regulatory, legal and tax requirements. We also depend on our information technology infrastructure for communications among our personnel, contractors, consultants and suppliers. System failures or outages could materially compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting, and could otherwise compromise the security of sensitive information, including personal information and health information. In addition, our remediation efforts for system failures, outages, or security breaches may not be successful. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information, including personal information and health information. In addition, we depend on third parties to operate and support our information technology systems. Failure by these providers to adequately deliver the contracted services could have an adverse effect on our business, which in turn may materially adversely affect our operating results and financial condition. We are subject to a variety of stringent and changing privacy and data security laws, regulations and standards, as well as contractual obligations related to data privacy and security, and our actual or perceived failure to comply with them could harm our business and reputation and subject us to significant fines and liability. We maintain a quantity of sensitive information, including confidential business and patient health information in connection with our clinical trials, and are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. For example, the European Union GPDR, or the GDPR, and United Kingdom General Data Protection Regulation, or the UK GDPR, which apply extraterritorially, and impose several strict requirements for controllers and processors of personal information, including higher standards for obtaining consent from individuals to process their personal information, increased requirements pertaining to the processing of special categories of personal information (such as health information) and pseudonymized (i. e., key- coded) data, and transfer of personal information from the EEA / UK / Switzerland to countries not deemed to have adequate data protections laws (e. g., the United States as of January 1, 2023, although active treaty negotiations between the United States and the EU may change that status in 2023). The GDPR also provides that countries in the EEA may establish their own laws and regulations further restricting the processing of certain personal information, including genetic data, biometric data, and health data. Companies that must comply with the GDPR and UK GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to € 20 million or £ 17 million (approximately $ 22. 6 million), respectively, or four percent of the annual global revenues of the noncompliant company , whichever is greater . **72** In the United States, in addition to HIPAA, various federal and state regulators have adopted, or are considering adopting, laws and regulations concerning personal information and data security. Certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to personal information than federal, international or other state laws, and such laws may differ from each other, all of which may complicate compliance efforts. For example, California, which continues to be a critical state with respect to evolving consumer privacy laws after enacting the California Consumer Privacy Act, or CCPA, later amended by ballot measure through the California Privacy Rights Act, or CPRA. The CPRA took effect in January 2023 and enforcement will begin on July 1, 2023, subject to regulations promulgated through a newly created enforcement agency called the California Privacy Protection Agency, or CPPA. Failure to comply with the CCPA and the CPRA may result in significant civil penalties, injunctive relief, or statutory or actual damages as determined by the CPPA and California Attorney General through its investigative authority. Notably, comparable consumer privacy laws are set to take effect in 2023 in other states including the Virginia Consumer Data Protection Act (effective January 1, 2023), the Colorado Privacy Act and the Connecticut Data Privacy Act (both effective July 1, 2023), and the Utah Consumer Privacy Act (effective December 31, 2023). Compliance with this new privacy legislation may result in additional costs and expense of resources to maintain compliance. There is also discussion in the United States of a new comprehensive federal data privacy law to which we would become subject if it is enacted. We cannot provide assurance that (i) current or future legislation will not prevent us from generating or maintaining personal information, or (ii) that patients will consent to the use of their personal information (as necessary). Either of these circumstances may prevent us from undertaking or publishing essential research and development, manufacturing, and commercialization, which could have a material adverse effect on our business, results of operations, financial condition, and prospects. Federal, state, and foreign government requirements include obligations of companies to notify regulators and / or individuals of security breaches or other similar reportable incidents experienced by us, our vendors, contractors, and organizations with whom we had specific contractual obligations to protect our data. Further, the improper access to, use of, or disclosure of our data or a third- party' s personal information could subject us to individual or consumer class action litigation and governmental investigations and proceedings by federal, state, and local regulatory entities in the United States and by international regulatory entities. Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time- intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules and possible government oversight. In addition to

government regulation, privacy advocates and industry groups have and may in the future propose self- regulatory standards from time to time. These and other industry standards may legally or contractually apply to us, or we may elect to comply with such standards. It is possible that if our practices are not consistent or viewed as not consistent with legal and regulatory requirements, including changes in laws, regulations and standards or new interpretations or applications of existing laws, regulations and standards, we may become subject to audits, inquiries, whistleblower complaints, adverse media coverage, investigations, loss of export privileges, or severe criminal or civil sanctions, all of which may have a material adverse effect on our business, operating results, reputation, and financial condition. All of these evolving compliance and operational requirements impose significant costs, such as costs related to organizational changes, implementing additional protection technologies, training employees and engaging consultants, which are likely to increase over time. In addition, such requirements may require us to modify our data processing practices and policies, distract management or divert resources from other initiatives and projects, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Any failure or perceived failure by us to comply with any applicable federal, state or similar foreign laws and regulations relating to data privacy and security could result in damage to our reputation, as well as proceedings or litigation by governmental agencies or other third parties, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, sanctions, awards, injunctions, penalties or judgments. Any of the foregoing could have a material adverse effect on our business, results of operations, financial condition and prospects. We and our strategic partners that we rely on may be adversely affected by natural disasters, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster. Natural disasters could severely disrupt our operations or the operations of our third party manufacturers' facilities and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage, global epidemic, pandemic or contagious disease, or other event occurred that prevented us from using all or a significant portion of our headquarters or research laboratory, that damaged critical infrastructure, such as our third party manufacturers' facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Substantially all of our current supply of product candidates are located at a single third party manufacturer' s facilities, and we do not have any existing back- up facilities in place or plans for such back- up facilities. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects. We may be subject to securities litigation, which is expensive and could divert management attention. Our stock price is volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management' s attention from other business concerns, which could seriously harm our business. If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our stock, our stock price and trading volume could decline. If securities or industry analysts do not publish research or reports about our business, or publish negative or misleading reports about our business, our stock price and trading volume could decline. The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us or provide favorable coverage. If one or more of the analysts who cover us downgrade our stock or change their opinion of our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our stock price or trading volume to decline. 71