Risk Factors Comparison 2024-04-01 to 2023-03-30 Form: 10-K

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Our business is subject to numerous risks. You should carefully consider the following risks and all other information contained in this Annual Report on Form 10- K, as well as general economic and business risks, together with any other documents we file with the SEC. If any of the following events actually occur or risks actually materialize, it could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our common stock to decline. Summary of Risk Factors ● We **may not be successful in identifying and implementing any strategic transaction for OLINVYK and any strategic transactions that we may consummate in the future could have negative consequences. ● If we successfully consummate any transaction from our strategic assessment, including, but not limited to, a sale, divestiture of assets and / or licensing of OLINVYK, we may fail to realize all of the anticipated benefits of the transaction, those benefits may take longer to realize than expected, or we may encounter integration difficulties. ● If a strategic transaction for OLINVYK is not consummated, our board of directors may decide to pursue a dissolution and liquidation. In such an event, the amount of cash available for distribution to our stockholders will depend heavily on the timing of such liquidation as well as the amoubt of cash that will need to be reserved for commitments and contingent liabilities. ● We may become involved in litigation, including securities class action litigation, that could divert management' s attention and harm the Company' s business and insurance coverage may not be sufficient to cover all costs and damages. ● We** have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability. ● Our prospects are highly dependent on **sales of OLINVYK and** the successful commercialization of ~~OLINVYK~~ **our other product candidates** . To the extent ~~OLINVYK is not commercially~~ **we are unable to** ~~successful~~ **successfully complete development, obtain regulatory approval for or commercialize one or more of our product candidates, or if we experience delays in doing so** , our business, financial condition and results of operations may be materially adversely affected, and the price of our common stock may decline. ● We will need substantial additional funding, which may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts and may not be able to continue as a going concern. ● If we are unable to comply with the applicable continued listing requirements or standards of The Nasdaq Stock Market, including the minimum bid price requirement and minimum stockholders' equity requirement, Nasdaq could delist our common stock. ● Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability. ● ~~The ongoing COVID- 19 pandemic, and the efforts to mitigate it, could materially affect our operations, as well as the business or operations of third parties with whom we conduct business. ● The ongoing COVID- 19 pandemic, and the efforts to mitigate it, may negatively impact the commercialization and market acceptance of OLINVYK. ●~~ OLINVYK or any of our other product candidates for which we obtain approval may fail to achieve the degree of market acceptance by physicians, patients, third- party payors, and others in the medical community necessary for commercial success. ● We could face legal or regulatory actions related to the sales, marketing and promotion of OLINVYK to healthcare professionals and healthcare institutions. ● ~~If we are unable to maintain or expand our manufacturing, sales, marketing, and distribution capabilities or to enter into agreements with third parties to produce, market, sell, and distribute our product candidates, we may not be successful in commercializing OLIVNYK or any of our other product candidates if and when they are approved. ●~~ We face substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than we do. ● If we are not able to obtain, or if there are delays in obtaining regulatory approval of ~~OLINVYK for any indications in foreign jurisdictions, or~~ **our** ~~regulatory approval of our other~~ product candidates, we will not be able to market ~~OLINVYK in other jurisdictions or~~ **our** ~~market our other~~ product candidates at all, and our ability to generate revenue will be materially impaired. ● OLINVYK has been classified as a Schedule II controlled substance, and the making, use, sale, importation, exportation and distribution of controlled substances are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies which may make the successful commercialization and market acceptance more difficult. ● We are early in our development efforts and have only one product, OLINVYK, for which we have received marketing approval from the FDA. If **sales of OLINVYK are unsuccessful, or if** we are unable to ~~successfully commercialize OLINVYK, or if we are unable to~~ complete development **and commercialize any** of our other product candidates, or if we experience significant delays in doing so, our business will be materially harmed. ● Nonclinical and clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates. ● We may be unable to obtain regulatory approval for our product candidates under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of our product candidates and adversely impact our potential to generate revenue, our business and our results of operations. ● We rely, and expect to continue to rely, on third parties to conduct our nonclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or complying with applicable regulatory requirements. ● We contract with third parties for the manufacture of commercial supply of OLIVNYK and for clinical supply of our other product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of OLIVNYK or our other product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or ~~commercialization~~ **sales** efforts. ~~33~~ **29** ● Materials necessary to manufacture our product or product candidates may not be available on commercially reasonable terms, or at all, which may delay the development and

commercialization of our product or product candidates. ● If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired. ● In the future, we expect to expand our development, regulatory, manufacturing, sales, marketing, and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. ● We may not have cash available to us in an amount sufficient to enable us to make interest or principal payments on our indebtedness when due. ● We are subject to certain terms and restrictive covenants which, if breached, could have a material adverse effect on our business and prospects. ● We maintain significant inventories of OLINVYK, and in **2023 and** 2022 we recorded an inventory valuation adjustment, primarily for slow- moving or obsolete inventory related to OLINVYK, as well as an increase in returns reserve from our wholesalers. Risks **Related to our Strategic Review ProcessWe may not be successful in identifying and implementing any strategic transaction for OLINVYK and any strategic transactions that we may consummate in the future could have negative consequences. In April 2024, we announced that we are undertaking a review of strategic alternatives for OLINVYK focused on maximizing stockholder value, including, but not limited to, sale, out- license, divestiture of assets, in- licensing, discontinuation of US commercial sales or other strategic transaction. We expect to devote substantial time and resources to exploring strategic alternatives that our Board of Directors believes will maximize stockholder value. Despite devoting significant efforts to identify and evaluate potential strategic alternatives, there can be no assurance that this strategic review process will result in us pursuing any transaction or that any transaction, if pursued, will be completed on attractive terms or at all. We have not set a timetable for completion of this strategic review process, and our Board of Directors has not approved a definitive course of action. Additionally, there can be no assurances that any particular course of action, business arrangement or transaction, or series of transactions, will be pursued, successfully consummated or lead to increased stockholder value or that we will make any additional cash distributions to our stockholders. The process of continuing to evaluate these strategic options may be very costly, time- consuming and complex and we have incurred, and may in the future incur, significant costs related to this continued evaluation, such as legal and accounting fees and expenses and other related charges. We may also incur additional unanticipated expenses in connection with this process. A considerable portion of these costs will be incurred regardless of whether any such course of action is implemented or transaction is completed. Any such expenses will decrease the remaining cash available for use in our business. In addition, potential counterparties in a strategic transaction involving our company may place minimal or no value on our assets and our public listing. Further, should we resume the development of our product candidates, the development and any potential commercialization of our product candidates will require substantial additional cash to fund the costs associated with conducting the necessary preclinical and clinical testing and obtaining regulatory approval. Consequently, any potential counterparty in a strategic transaction involving our company may choose not to spend additional resources and continue development of our product candidates and may attribute little or no value, in such a transaction, to those product candidates. 30In addition, any strategic business combination or other transactions that we may consummate in the future could have a variety of negative consequences and we may implement a course of action or consummate a transaction that yields unexpected results that adversely affects our business and decreases the remaining cash available for use in our business or the execution of our strategic plan. Any potential transaction would be dependent on a number of factors that may be beyond our control, including, among other things, market conditions, industry trends, the interest of third parties in a potential transaction with us, obtaining stockholder approval and the availability of financing to third parties in a potential transaction with us on reasonable terms. Any failure of such potential transaction to achieve the anticipated results could significantly impair our ability to enter into any future strategic transactions and may significantly diminish or delay any future distributions to our stockholders. If we are not successful in setting forth a new strategic path for the Company, or if our plans are not executed in a timely fashion, this may cause reputational harm with our stockholders and the value of our securities may be adversely impacted. In addition, speculation regarding any developments related to the review of strategic alternatives and perceived uncertainties related to the future of the Company could cause our stock price to fluctuate significantly. Even if we successfully consummate any transaction from our strategic assessment, including, but not limited to, a sale, divestiture of assets and / or licensing of OLINVYK, we may fail to realize all of the anticipated benefits of the transaction, those benefits may take longer to realize than expected, or we may encounter integration difficulties. Our ability to realize the anticipated benefits of any potential business combination or any other result from our strategic assessment, are highly uncertain. Any anticipated benefits will depend on a number of factors, including our ability to integrate with any future business partner and our ability to generate future stockholder value in the platform we may elect to pursue. The process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The failure to meet the challenges involved and to realize the anticipated benefits of any potential transaction could adversely affect our business and financial condition. If we are successful in completing a strategic transaction for OLINVYK, we may be exposed to other operational and financial risks. Although there can be no assurance that a strategic transaction will result from the process we have undertaken to identify and evaluate strategic alternatives for OLINVYK, the negotiation and consummation of any such transaction will require significant time on the part of our management, and the diversion of management' s attention may disrupt our business. The negotiation and consummation of any such transaction may also require more time or greater cash resources than we anticipate and expose us to other operational and financial risks, including: ● increased near- term and long- term expenditures; ● exposure to unknown liabilities; ● higher than expected acquisition or integration costs; ● incurrence of substantial debt or dilutive issuances of equity securities to fund future operations; ● write- downs of assets or goodwill or incurrence of non- recurring, impairment or**

other charges; ● increased amortization expenses; ● difficulty and cost in combining the operations and personnel of any acquired business with our operations and personnel; ● impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership; ● inability to retain key employees of our company or any acquired business; and ● possibility of future litigation. Any of the foregoing risks could have a material adverse effect on our business, financial condition and prospects. 31If a strategic transaction is not consummated, our Board of Directors may decide to pursue a dissolution and liquidation. In such an event, the amount of cash available for distribution to our stockholders will depend heavily on the timing of such liquidation as well as the amount of cash that will need to be reserved for commitments and contingent liabilities. There can be no assurance that a strategic transaction will be completed. If a strategic transaction is not completed, our Board of Directors may decide to pursue a dissolution and liquidation. In such an event, the amount of cash available for distribution to our stockholders will depend heavily on the timing of such decision and, with the passage of time the amount of cash available for distribution will be reduced as we continue to fund our operations. In addition, if our Board of Directors were to approve and recommend, and our stockholders were to approve, a dissolution and liquidation, we would be required under Delaware corporate law to pay our outstanding obligations, as well as to make reasonable provision for contingent and unknown obligations, prior to making any distributions in liquidation to our stockholders. As a result of this requirement, a portion of our assets may need to be reserved pending the resolution of such obligations and the timing of any such resolution is uncertain. In addition, we may be subject to litigation or other claims related to a dissolution and liquidation. If a dissolution and liquidation were pursued, our Board of Directors, in consultation with our advisors, would need to evaluate these matters and make a determination about a reasonable amount to reserve. Accordingly, holders of our common stock could lose all or a significant portion of their investment in the event of a liquidation, dissolution or winding up. Our ability to consummate a strategic transaction depends on our ability to retain our employees required to consummate such transaction. Our ability to consummate a strategic transaction depends upon our ability to retain our employees required to consummate such a transaction, the loss of whose services may adversely impact the ability to consummate such transaction. The strategic review process is supported by our deep and broad experience at the board, executive management, and supporting staff levels. Our cash conservation activities may yield unintended consequences, such as attrition beyond our reduction in workforce and reduced employee morale, which may cause remaining employees to seek alternative employment. Our ability to successfully complete a strategic transaction depends in large part on our ability to retain certain of our remaining personnel. If we are unable to successfully retain our remaining personnel, we are at risk of a disruption to our exploration and consummation of a strategic alternative as well as business operations. Any future growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Due to our limited resources, we may not be able to effectively manage our operations or recruit and retain qualified personnel, which may result in weaknesses in our infrastructure and operations, risks that we may not be able to comply with legal and regulatory requirements, and loss of employees and reduced productivity among remaining employees. Our future financial performance and, should we resume development, our ability to develop our product candidates or additional assets will depend, in part, on our ability to effectively manage any future growth or restructuring, as the case may be. We may become involved in litigation, including securities class action litigation, that could divert management' s attention and harm the company' s business, and insurance coverage may not be sufficient to cover all costs and damages. In the past, litigation, including securities class action litigation, has often followed certain significant business transactions, such as the sale of a company or announcement of any other strategic transaction, or the announcement of negative events, such as negative results from clinical trials. These events may also result in investigations by the SEC. We may be exposed to such litigation even if no wrongdoing occurred. Litigation is usually expensive and diverts management' s attention and resources, which could adversely affect our business and cash resources and our ability to consummate a potential strategic transaction or the ultimate value our stockholders receive in any such transaction. 32Risks Related to Our Financial Position and Capital Needs We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability. Since inception, we have incurred significant operating losses. Our net loss was $ **40. 3 million and $** 53. 7 ~~million and $ 51. 6~~ million for the years ended December 31, **2023 and** 2022 ~~and 2021~~, respectively. As of December 31, ~~2022~~ **2023**, we had an accumulated deficit of $ ~~547~~ **588**. ~~8~~ **1** million. To date, we have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. We have devoted substantially all of our financial resources and efforts to research and development, including nonclinical studies and clinical trials. In August 2020, the FDA granted approval for OLIVNYK as a treatment in the United States for the management of acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. ~~Accordingly, we are currently focusing a substantial portion~~ **We have not generated significant revenue from the sale** of ~~our~~ **OLINVYK, and in April 2024, we announced the reduction of commercial support for OLINVYK. We have suspended marketing and product development** efforts **with respect to** ~~on the commercialization of~~ OLINVYK **as we evaluate potential strategic and financing alternatives for Trevena. We will continue to sell OLINVYK through our existing sales and distribution channels** ~~, which commenced~~ **but we may not be successful** in ~~the first quarter~~ **generating additional sales** of ~~2021~~ **OLINVYK**. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase if we: ● **are unable to identify strategic alternatives for** ~~commercialize~~ **commercializng** OLINVYK **or our other product candidates** in the United States; ● build out our sales, marketing and distribution capabilities and scale up external manufacturing capabilities to commercialize ~~OLINVYK, and~~ any ~~other~~ product candidates that we choose not to license to a third party and for which we may obtain regulatory approval; ●

conduct clinical trials for our other product candidates; ● seek regulatory approvals for any product candidates that successfully complete clinical trials; ● seek to identify additional product candidates; ~~34~~ ● maintain, expand, and protect our intellectual property portfolio; ● hire additional sales, marketing, medical, clinical and scientific personnel; and ● add operational, financial, and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts. To become and remain profitable, we must succeed in raising substantial additional funding for the Company and developing and commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing nonclinical testing and clinical trials of our product candidates, identifying additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates, and manufacturing, marketing, and selling OLINVYK and any products **or product candidates** for which we may obtain regulatory approval. We are only in the preliminary stages of some of these activities and have not begun others. We may never succeed in these activities and, even if we do, our future profitability will depend upon the size of any markets in which our product candidates have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third- party payors and adequate market share for our products in those markets. ~~Because~~ **33Because** of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses, whether we will have sufficient funding available to or when, or if, we will be able to achieve profitability. If, for example, we are required by the FDA or foreign regulatory authorities to perform studies in addition to those we currently anticipate conducting, or if there are any delays in completing our clinical trials, making necessary regulatory filings, or the development of any of our product candidates, our expenses could increase. Absent substantial additional fundraising, the level and extent of our clinical and, if approved, commercial efforts may lead to a delay in our ability to achieve profitability. Even 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 depress the value of our company and could impair our ability to raise capital, expand our business, continue our development efforts, diversify our product offerings, or even continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment. Our prospects are highly dependent on the **sales of OLINVYK and the** successful commercialization of ~~OLINVYK~~ **our other product candidates** . To the extent ~~OLINVYK is not commercially~~ **we are unable to** ~~successful~~ **successfully complete clinical development, obtain regulatory approval for or commercialize one or more of our product candidates, or if delays in doing so** , our business, financial condition and results of operations may be materially adversely affected, and the price of our common stock may decline. ~~OLINVYK~~ **Our future success and ability to generate significant revenue from our product candidates** is **dependent on our ability to successfully develop, obtain regulatory approval for and commercialize one** ~~our~~ **or more of our product candidates. All of our** ~~only drug that has been approved for sale and it has only been approved as a treatment in the~~ **other product candidates are** ~~United States for the management of acute pain~~ in ~~adults severe enough to~~ **earlier stages of development and will** require **substantial additional investment for manufacturing, preclinical testing, clinical development, regulatory review** ~~an~~ **and approval in one** ~~intravenous opioid analgesic and for~~ **or** ~~whom alternative treatments are inadequate~~ **more jurisdictions. If any of our product candidates encounter safety or efficacy problems, development delays or regulatory issues or other problems, our development plans and business would be materially harmed** . We **may not have the financial** ~~are currently focusing a significant portion of our activities and~~ resources ~~on OLINVYK and we are highly dependent upon the successful commercialization of OLINVYK in the United States. Successful commercialization of OLINVYK is subject~~ to **continue** ~~many risks. While we have established our commercial team and have hired our U. S. sales force, we may need to further expand and develop~~ **development of our product candidates** ~~, and at times restructure the team in order to successfully commercialize OLINVYK~~ . Even if ~~we~~ **clinical trials** are ~~successful in developing~~ **completed, we may experience other issues that may delay** ~~our~~ **or prevent regulatory approval of, or our ability to commercialize, our product candidates. Our product candidates will require additional, time- consuming development efforts prior to** commercial ~~team~~ **sale** , **including preclinical studies, clinical trials and approval by** ~~there~~ **the FDA and applicable foreign regulatory authorities. All product candidates** are **prone** ~~many factors that could cause the commercialization of OLINVYK~~ to **the risks** ~~be unsuccessful, including a number~~ of ~~factors~~ **failure** that are **inherent** ~~outside our control. Because OLINVYK is an opioid agonist and is the first new chemical entity~~ in **pharmaceutical** ~~the IV opioid drug class in decades, it is especially difficult to estimate OLINVYK's market potential for its approved indication. We do not know if our expectations of the market for this~~ product ~~will be accurate. Additionally, hospitals may be unwilling to add OLINVYK to their formularies or physicians may be unwilling to prescribe OLINVYK. Further, any negative publicity related to OLINVYK, or negative~~ development ~~for OLINVYK in our post- marketing commitments, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of OLINVYK. 35In addition, our commercialization efforts could be adversely affected by the effects of public health threats~~ , including ~~pandemics~~ **the possibility that** such **product candidate** ~~as the COVID- 19 pandemic and the efforts to mitigate them. In light of the lengthy duration of the pandemic, we continue to expect that sales of OLINVYK may be negatively impacted by changes in commercial practices resulting from COVID- 19, such as the transition to telemedicine, possible decreases in initial diagnoses, deferral of elective procedures, and decreased access to certain market segments. The ultimate effects of COVID- 19, and the duration thereof, are difficult to assess or predict at this time and no assurances can be given that the pandemic~~ will not ~~have a significant impact on~~ **be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure stockholders that any such products that are approved will be manufactured** ~~our~~ **or** ~~ability to~~ **produced economically, successfully** ~~commercialize~~ **commercialized** ~~OLINVYK, which in turn could have a material adverse effect on our~~ **or widely accepted in** ~~business, results of operations, financial condition and prospects. If~~ the **marketplace or be more effective** ~~commercialization of OLINVYK is less successful~~ than ~~expected, our stock price could decline significantly and the~~ **other commercially available alternatives** ~~long- term success of the product and our company could be harmed~~ . We will need

substantial additional funding, which may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts and may not be able to continue as a going concern. As of December 31, ~~2022~~ **2023**, we had cash and cash equivalents of $ ~~38~~ **33**. ~~3~~ **0 million and restricted cash of $ 0. 5** million. Based upon our current operating plan, we believe that our available cash and cash equivalents will **not** be sufficient to fund our planned operations and capital expenditure requirements ~~into~~ **for one year after** the **date** ~~fourth quarter~~ of ~~2023~~ **this filing and therefore management has concluded that substantial doubt exists about our ability to continue as a going concern**. Although we plan and budget funding for our operations, it is possible that we may have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. **We** ~~Over the next several years, we~~ expect to incur significant expenses in connection with our current operations ~~, as we commercialize OLINVYK and continue the clinical trials of, and seek marketing approval for, our other drug candidates~~. Furthermore, we will continue to incur costs associated with operating as a public company ~~,~~ **and** hiring personnel **,** as needed. Accordingly, we will need to obtain substantial additional funding for these efforts; we would seek to obtain this funding through the sale of equity, the incurrence of debt, and / or other sources, including potential collaborations. Ultimately, we may be unable to raise ~~additional~~ **34additional** funds or enter into such other arrangements when needed, on favorable terms, or at all. If we fail to raise additional capital or enter into such arrangements as, and when, needed, we could be forced to: ● significantly delay, scale back, or discontinue our operations, development programs, and / or any current or future commercialization efforts; ● relinquish, or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves; ● seek collaborators for one or more of our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or ● may be unable to continue as a going concern and could cease operations altogether. The extent of our future capital requirements will depend on many factors, including: ● our ability to ~~successfully~~ **find strategic alternatives for** ~~commercialize~~ **commercializing** OLINVYK in the United States; ● the scope, progress, results and costs of nonclinical development, laboratory testing, and clinical trials for our product candidates, including TRV045 ~~, TRV250,~~ and TRV734 ~~,~~; ● the number and development requirements of other product candidates that we pursue; ● the costs, timing, and outcome of regulatory review of any product candidates, both in the United States and in territories outside the United States; ~~36~~ ● the costs and timing of ~~commercializing OLINVYK and~~ any future commercialization activities, including product manufacturing, marketing, sales, and distribution, for any of our product candidates for which we receive marketing approval; ● the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval; ● our ability to enter into collaborative agreements for the development and commercialization of our product candidates; ● any product liability or other lawsuits related to our products or operations; ● the expenses needed to attract and retain skilled personnel; ● the costs involved in preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property rights, and defending any intellectual property- related claims, both in the United States and in territories outside of the United States; and ● the impact of ~~the COVID- 19 pandemic and~~ any future epidemics and pandemics ~~that may arise in the future~~. Identifying potential product candidates and conducting nonclinical testing and clinical trials is a time- consuming, expensive and uncertain process that takes years to complete. Despite these efforts, we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales for our product candidates. In addition, our other product candidates, if approved, may not achieve commercial success or meet our expectations. Our ability to generate commercial revenue from sales of OLINVYK is unproven, and we do not expect **our** ~~any other products~~ **product candidates** to be commercially available for the foreseeable future, if at all. Accordingly, we will need to ~~continue~~ **35continue** to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all ~~. The risk that additional financing is unavailable is heightened by the sustained macro- economic disruption from the COVID- 19 pandemic. We cannot predict the extent or duration of the impact of the COVID- 19 pandemic on the capital markets~~. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. Furthermore, a systemic failure of the banking system in the United States or globally may result in a situation in which we lose our deposits, or access to our deposits, and are unable to obtain financing from other sources which could materially and adversely affect our business and financial condition. Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability. We are a biopharmaceutical company with a limited operating history. Our activities to date have been limited to, among other things, organizing and staffing our company, business planning, raising capital, developing our product platform, identifying potential product candidates, undertaking nonclinical studies, and conducting clinical trials of our product candidates. With the exception of OLINVYK, our product candidates are in early stages of development. We have ~~only recently begun to conduct sales, marketing, and distribution activities to commercialize OLINVYK, and we have~~ not yet demonstrated the ability to generate significant revenue from the sale of OLINVYK. Consequently, any predictions you make about our future success or viability may not be as reliable as they could be if we had a longer and more established operating history. We have encountered, and will continue to encounter, risks and difficulties frequently experienced by growing companies in a rapidly developing and changing industry, such as the biopharmaceutical industry, including challenges in forecasting accuracy, determining appropriate investments of our limited resources, gaining market acceptance of our products, if approved, managing a complex regulatory landscape and developing new product candidates. Our current ~~37operating~~ **operating** model may require changes in order for us to scale our operations efficiently. You should consider our business and prospects in light of the risks and difficulties we face as a company focused on developing products in the fields of biopharmaceuticals and biotechnology. We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any past quarterly or annual periods as indications of future operating performance. ~~The COVID- 19 pandemic and the efforts to mitigate it could~~

~~materially affect our operations, as well as the business or operations of third parties with whom we conduct business. Our business and its operations, including but not limited to clinical development, sales and marketing efforts, supply chain operations, research and development activities, could be adversely affected by health epidemics, such as the COVID- 19 pandemic, in regions where we have business operations, and such health epidemics could cause significant disruption in the operations of third parties upon whom we rely. We have implemented work- from- home policies for all headquarter employees. The effects of the COVID- 19 pandemic may negatively impact productivity, disrupt our business, delay our clinical programs and timelines and adversely affect our commercialization and market acceptance of OLINVYK, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. These and similar, and perhaps more severe, disruptions in our operations could negatively impact our business, operating results and financial condition. In addition, our clinical trials have been, and may continue to be, affected by the COVID- 19 pandemic. Clinical site initiation and patient enrollment may be delayed due to prioritization of hospital resources toward the COVID- 19 pandemic. Also, some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID- 19 and adversely impact our clinical trial operations. Limitations on global international travel and the impact of COVID- 19 in other countries may delay key trial activities, including necessary interactions with regulators, ethics committees and other important agencies and contractors. We may be faced with limitations in employee resources that would otherwise be focused on the conduct of clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people. Any of the above could delay our planned clinical trials or prevent us from completing these clinical trials at all and harm our ability to obtain approval for our product candidates. Moreover, we may experience additional disruptions that could severely impact our business and development activities, including, but not limited to, strain on our suppliers and other third parties, possibly resulting in supply disruptions of our product candidates for nonclinical or clinical development and potential future clinical trials we expect to initiate, decrease in clinical enrollment in any clinical trials we initiate and the ability to raise capital when needed on acceptable terms, if at all. Disruptions in our operations or supply chain, whether as a result of restricted travel, quarantine requirements or otherwise, could negatively impact our ability to proceed with our clinical trials, nonclinical development and other activities and delay our ability to receive product approval and generate revenue. The extent to which COVID- 19 impacts our results will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of COVID- 19, the emergence of any new mutations or variants of the virus, administration rates and effectiveness of vaccines and their effectiveness, the duration of the outbreak, travel restrictions imposed by the United States and other countries, business closures or business disruption in the United States and other countries, and the actions taken throughout the world, including in our markets, to contain COVID- 19 or treat its impact. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our nonclinical development efforts, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID- 19 situation closely. 38The COVID- 19 pandemic may negatively impact the commercialization and market acceptance of OLINVYK. The COVID- 19 pandemic may have an adverse impact on our ability to successfully commercialize and secure market acceptance of OLINVYK. As a result of the COVID- 19 pandemic, we or our employees, contractors, suppliers, and other partners may be prevented from conducting normal business activities for an indefinite period of time, including due to continuation of government- imposed quarantines, stay- at- home orders, travel restrictions, mandated business closures and other public health safety measures. If the spread of COVID- 19 and the public safety measures taken by various governments continue, the successful commercialization and market acceptance of OLINVYK may be hindered by various factors, including the overall economy, cancellations in elective surgeries, challenges in hiring employees who are necessary to support continued commercialization, difficulties in meeting with healthcare providers, pharmacists or others involved in prescribing and formulary decisions, limited access to healthcare providers' offices, conducting necessary trainings of such new employees, attending and presenting at various conferences or other programs, delays in coverage decisions from Medicare and third- party payors, interruptions or delays in our commercial supply chain and increases in the number of uninsured or underinsured patients. The extent to which the COVID- 19 pandemic will impact our efforts to successfully commercialize and secure market acceptance of OLINVYK is uncertain and will depend upon future developments. We are monitoring the situation and taking steps to minimize the disruption of the COVID- 19 pandemic, but there can be no assurance that such actions will be successful, which could have a negative impact on our ability to successfully commercialize OLINVYK.~~ Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be ~~limited~~We -- **limited. We** have incurred substantial losses during our history. We do not anticipate generating revenue from sales of products for the foreseeable future, if ever, and we may never achieve profitability. To the extent that we continue to generate tax losses, unused losses generated in tax years ending on or prior to December 31, 2018 will carry forward to offset future taxable income, if any, until such unused losses expire. Unused tax losses generated after December 31, 2018 under the Tax Act will not expire and may be carried forward indefinitely, but will be deductible only to the extent of 80 % of current taxable income in any given year. It is uncertain if and to what extent various states will conform to the Tax Act. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), if a corporation undergoes an " ownership change, " which is 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 and other pre change tax attributes to offset its post change income or taxes may be limited. We have not completed an analysis to determine whether we have experienced an ownership change. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership. Similar provisions of state tax law may also apply to limit our use of accumulated state tax attributes. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or

otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, even if we attain profitability, we may be unable to use all or a material portion of our net operating losses and other tax attributes, which could adversely affect our future cash flows. As of December 31, ~~2022~~ **2023** , we had federal net operating loss carryforwards of approximately $ ~~188~~ **226** . ~~7~~ **5** million that could be limited if we have experienced, or if in the future we experience, an ownership change. ~~39We~~ **36We** may not have cash available to us in an amount sufficient to enable us to make interest or principal payments on our indebtedness when due. **An** ~~Through an~~ indirect subsidiary **(" SPV2 ")** , ~~we~~ entered into a royalty- based loan agreement, or the Loan Agreement, with R- Bridge ~~Healthcare~~ Investment ~~Advisory~~ , **Four Pte.** Ltd., or R- Bridge, pursuant to which we may incur up to $ 40. 0 million of indebtedness. The repayment of all borrowings, interest and other related payments under the Loan Agreement are ~~guaranteed by us and~~ secured by ~~substantially all of our assets associated with our license agreement with Nwha,~~ the Chinese intellectual property related to OLINVYK **and associated with our license agreement with Nhwa,** and deposit accounts established to hold any amounts received by ~~us~~ **SPV2** that are required to be used to ~~reapy~~ **repay** amounts ~~outstanding under~~ **in accordance with** the Loan Agreement. Our ability to make ~~scheduled~~ **any royalty** payments **from U. S. sales as further provided in** ~~of the principal of, to pay interest on or to refinance our indebtedness under~~ the Loan Agreement depends on our future performance, which is subject to regulatory, economic, financial, competitive and other factors beyond our control. We are a biopharmaceutical company that has not yet generated profit from product sales. We expect to continue to incur losses from our infrastructure and personnel to support our commercialization and product development efforts and operations. Accordingly, our business may not generate cash flow from operations in the future sufficient to ~~service our indebtedness under the Loan Agreement and~~ make ~~necessary~~ capital expenditures **necessary to general royalty payments** . If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity capital on terms that may be onerous or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms. If ~~we~~ **SPV2** ~~fail~~ **fails** to satisfy ~~our~~ **its** debt obligations under the Loan Agreement, it could result in an event of default and, as a result, R- Bridge could accelerate all of ~~the amounts due~~ **its rights and remedies** under the Loan Agreement ~~,~~ including ~~a premium in certain cases. In the event of any such acceleration of amounts due as a result of an event of default~~ , **but** ~~we may~~ not **limited** ~~have sufficient funds or may be unable~~ to ~~arrange for additional financing to repay our~~ **, foreclosing on the Chinese intellectual property that secures the** indebtedness ~~. In addition, R- Bridge could seek to enforce its respective security interests in certain assets~~ . See Note 7 – Loans Payable to the financial statements included in Part II of this Annual Report on Form 10- K for a more specific description of the Loan Agreement. We **may not satisfy the milestones or conditions set forth in our Loan Agreement with R- Bridge in order to draw down additional funding on our royalty- based loan. The second tranche of term loans (the " Second Tranche ") under our Loan Agreement with R- Bridge, in an amount up to $ 10. 0 million, may only be drawn, subject to the achievement of either a commercial or financing milestone as set forth in the Loan Agreement. We believe the gross proceeds from the private placement in December 2023, in addition to other Permitted Financing, as such term is defined in the Loan Agreement, may satisfy the conditions for us to receive the Second Tranche under the Loan Agreement. However, there can be no assurance when, or if, we will receive the funds under the Second Tranche. Without the achievement of the required commercial or financing milestones and satisfaction of certain customary conditions, we will not be eligible to draw additional funds under the Second Tranche. If we are unable to draw down additional funding under the terms of the Loan Agreement, our business, financial condition and results of operation may be harmed, and we may be required to seek out alternative financing sources which, if available, may have less favorable terms. 37We** are subject to certain restrictive covenants pursuant to the Loan Agreement which, if breached, could have a material adverse effect on our business and prospects. The Loan Agreement contains certain customary affirmative covenants, including those relating to: use of proceeds ; maintenance of books and records ; financial reporting and notification ; compliance with laws ; and protection of our intellectual property. The Loan Agreement also contains certain customary negative covenants, ~~barring~~ **related to us** ~~our~~ **or SPV2** ~~subsidiary that is party to the Loan Agreement from~~ **entering** certain fundamental transactions ; issuing dividends and distributions (other than certain exceptions, including distributing the loan proceeds to us) ; incurring additional indebtedness outside of the ordinary course of business ; engaging in any business activity other than related to our license agreement relating to OLINVYK with our partner in China, Jiangsu Nhwa Pharmaceutical Co. Ltd, or Nhwa. ; and permitting any additional liens on the collateral provided to R- Bridge under the Loan Agreement. **As a result, the Loan Agreement may limit our ability to pursue strategic alternatives and react to changes in our business.** Our **and SPV2' s** failure to observe or breach these covenants could result in an event of default and, as a result, R- Bridge could accelerate all of the amounts then due **by SPV2** under the Loan Agreement, including a premium in certain cases, or otherwise give R- Bridge certain rights over us **or SPV2,** which would have an adverse effect on our business. In addition, R- Bridge could seek to enforce its respective security interests in certain assets. ~~40We~~ **We** maintain significant inventories of OLINVYK, and in **2023 and** 2022 we recorded an inventory valuation adjustment, primarily for slow- moving or obsolete inventory related to OLINVYK, as well as an increase in returns reserve from our wholesalers. We maintain significant inventories of OLINVYK and evaluate these inventories on a periodic basis for potential slow- moving or obsolete amounts on hand. During ~~2022~~ **2023** , we recognized an inventory valuation adjustment of $ ~~2~~ **0** . ~~1~~ **9** million for OLINVYK inventories of hand, due to uncertainty of commercial activities and future expected OLINVYK sales. During ~~2022~~ **2023** , we also recorded a $ 0. ~~4~~ **1** million returns reserve adjustment for OLINVYK to account for expected returns from our wholesalers. The inventory valuation adjustment and returns reserve adjustment were based upon our analysis of current OLINVYK inventory on hand and at our wholesalers, and the remaining shelf- life, in relation to our projected demand for the product. **Inventories are fully reserved as** ~~Our adjustments for slow- moving or obsolete inventory is subjective and requires forecasting~~ of **December 31,** ~~the future market demand for our products. Forecasting demand for OLINVYK following its launch in 2021~~ **2023 and** ~~, with~~ no ~~sales history, coupled with the~~

~~unpredictable commercial environment as a result of the COVID pandemic, particularly with respect to hospitals, has been difficult. We will continue to evaluate our inventories and amounts held at wholesalers on a periodic basis. The value of our inventories could be impacted if actual sales differ significantly from our estimates of future demand and if any significant, unanticipated changes in future product demand or market conditions occur. Any of these events, or a combination thereof, could result in~~ additional inventory **manufacturing is planned** ~~write- downs in future periods, or further adjustments to returns or other reserves, which could be material~~ . Risks Related to Ownership of Our Common Stock The trading price of the shares of our common stock has been and may continue to be volatile, and you may not be able to resell some or all of your shares at a desired price. Since our common stock commenced trading in January 2014, our stock price has been highly volatile, with closing stock prices ranging from a high of $ 339. 25 per share to a low of $ ~~1~~ **0** . ~~30~~ **41** per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors in our stock may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including: ● **sales** ~~the success of our commercialization~~ of OLIVNYK for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate; ● the status and cost of our post- marketing commitments for OLIVNYK; ● ~~the status and cost of development and commercialization of OLIVNYK in jurisdictions other than the United States; ●~~ actual or anticipated variations in our operating results; ● changes in financial estimates by us or by any securities analysts who might cover our stock; **38** ● the timing and results of our clinical trials for any of our **product candidates; ● the status and cost of development and commercialization of our other** product candidates; ● failure or discontinuation of any of our development programs; ● conditions or trends in our industry; ● changes in the structure of healthcare payment systems; ~~41~~ ● stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry; ● announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures; ● developments or disputes concerning patent applications, issued patents or other proprietary rights; ● announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us; ● capital commitments; ● investors' general perception of our company and our business; ● recruitment or departure of key personnel; ● announcements and expectations of additional financing efforts; ● public concern as to, and legislative action with respect to, genetic testing or other research areas of biopharmaceutical companies, the pricing and availability of prescription drugs, or the safety of drugs and drug delivery techniques; ● disruptions caused by man- made or natural disasters or public health pandemics or epidemics or other business interruptions, including, for example, the COVID- 19 pandemic; ● economic and political factors, including but not limited to economic and financial crises, wars, terrorism, and political unrest; and ● sales of our common stock, including sales by our directors and officers or specific stockholders. If we are not able to comply with the applicable continued listing requirements or standards of The Nasdaq Stock Market, Nasdaq could delist our common stock. Our common stock is currently listed on The Nasdaq Stock Market. In order to maintain that listing, we must satisfy minimum financial and other continued listing requirements and standards, including the Minimum Bid Price Rule (as discussed below) and those regarding director independence and independent committee requirements, minimum stockholders' equity, and certain corporate governance requirements. There can be no assurances that we will be able to comply with the applicable listing standards. We are required to maintain a minimum bid price of $ 1. 00 per share. On ~~December 21~~ **September 1** , ~~2021~~ **2023** , we received a notice from Nasdaq indicating that the Company was not in compliance with Nasdaq Listing Rule 5550 (a) (2), or the Minimum Bid Price Rule, because our common stock failed to maintain a minimum closing bid price of $ 1. 00 for 30 consecutive business days. ~~In~~ **39In** accordance with Nasdaq Marketplace Rule 5810 ~~©~~ **(c)** (3) (A), the Company was afforded an initial period of 180 calendar days, or until ~~June 20~~ **February 28** , ~~2022~~ **2024** , to regain compliance with the Minimum Bid Price Rule. ~~In June~~ **On March 1,** ~~2022~~ **2024** , **the Company** ~~we applied for and~~ received **a letter** ~~an extension to this period~~ from Nasdaq ~~,~~ **stating that the Company has not regained compliance** with **the Minimum Bid Price Rule and is not currently eligible for** a ~~new~~ **second 180- day extension** period ~~ending December 19~~ **because the Company does not comply with the $ 5** , **000** ~~2022 to regain compliance. On November 9~~ , ~~2022, we announced a 1-~~ **000 minimum stockholders' equity initial listing requirement** for ~~-25 reverse stock split~~ **The Nasdaq Capital Market. The Nasdaq letter noted that unless the Company timely requests an appeal** of **this determination to the Nasdaq Hearings Panel (the " Panel "),** the Company' s common stock **will be scheduled for delisting from The Nasdaq Capital Market. On March 5** , ~~and~~ **2024, the Company submitted a request for a hearing to appeal Nasdaq' s delisting determination. In response to the Company' s request for a hearing,** on ~~November 28~~ **March 5** , ~~2022~~ **2024** , ~~we~~ **the Company** received ~~notice~~ **a letter** from Nasdaq **granting** ~~that we had regained compliance with~~ the ~~Minimum Bid Price Rule~~ **Company' s request for a hearing on appeal and staying the delisting action noted in Nasdaq' s letter pending a final decision by the Panel and the expiration of any additional extension period granted by the Panel following the hearing. The Panel hearing is scheduled for May 2, 2024, at 10: 00 a. m. via video conference** . In the event that our common stock is delisted from The Nasdaq Stock Market and is not eligible for quotation or listing on another market or exchange, trading of our common stock could be conducted only in the over the counter market or on an electronic bulletin board established for unlisted securities such as the Pink Sheets or the OTC Bulletin ~~42Board~~ -- **Board** . In such event, it could become more difficult to dispose of, or obtain accurate price quotations for, our common stock, and there would likely also be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. Also, it may be difficult for us to raise additional capital if we are not listed on a major exchange. Such a de- listing would also likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. In the event of a de listing, we may take actions to restore our compliance with The Nasdaq Stock Market' s listing requirements, but we can provide no assurance that any such action taken by us would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below The Nasdaq Stock Market minimum bid price

requirement or prevent future non- compliance with The Nasdaq Stock Market' s listing requirements. If our common stock were delisted and determined to be a " penny stock, " a broker- dealer may find it more difficult to trade our common stock and an investor may find it more difficult to acquire or dispose of our common stock in the secondary market. If our common stock were removed from listing with The Nasdaq Capital Market, it may be subject to the " penny stock " rules of the Exchange Act. The Exchange Act defines a " penny stock " as an equity security that has a market price per share of less than $ 5. 00, subject to certain exceptions, such as any securities listed on a national securities exchange, which is the exception on which we currently rely. The penny stock rules require that prior to a transaction involving a penny stock, the broker- dealer must make a special written determination that the penny stock is a suitable investment for the purchaser and receive the purchaser' s written agreement to the transaction. If our common stock were delisted and determined to be a " penny stock, " a broker- dealer may find it more difficult to trade our common stock and an investor may find it more difficult to acquire or dispose of our common stock on the secondary market. We may be subject to securities class action and stockholder derivative litigation. We have in the past, and may in the future, become subject to class action and stockholder derivative litigation. We and our officers and directors, from time to time, could be subject to such lawsuits. If that were to occur, such suits and any resolution of such suits could result in substantial costs and divert management' s attention and resources from our business. This could have a material adverse effect on our business, operating results and financial condition. ~~Sales~~ **40Sales** of a substantial number of shares of our common stock could cause the market price of our common stock to drop significantly, even if our business is doing well. Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly. In addition, we have filed registration statements on Form S - 8 registering the issuance of shares of common stock subject to options or other equity awards issued or reserved for future issuance under our equity incentive plans. Shares registered under these registration statements on Form S - 8 are available for sale in the public market subject to vesting arrangements and exercise of existing options, the grant of new options in the future, and the restrictions of Rule 144 in the case of our affiliates. We are a " smaller reporting company " and, as a result of the reduced disclosure and governance requirements applicable to smaller reporting companies, our common stock may be less attractive to investors. We are a " smaller reporting company " as defined in Rule 12b- 2 promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not smaller reporting companies, including reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict ~~43if~~ **if** investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. The issuance of additional stock in connection with financings, acquisitions, investments, our stock incentive plans or otherwise will dilute all other stockholders. Our Certificate of Incorporation authorizes us to issue up to 200, 000, 000 shares of common stock and up to 5, 000, 000 shares of preferred stock with such rights and preferences as may be determined by our ~~board~~ **Board** of ~~directors~~ **Directors** . Subject to compliance with applicable rules and regulations, we may seek to expand the number of authorized common shares, and issue our shares of common stock or securities convertible into our common stock from time to time in connection with a financing, acquisition, investment, our stock incentive plans or otherwise. Any such issuance could result in substantial dilution to our existing stockholders and cause the trading price of our common stock to decline. Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result. There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our ~~board~~ **Board** of ~~directors~~ **Directors** has the authority to issue up to 5, 000, 000 shares of preferred stock. The ~~board~~ **Board** of ~~directors~~ **Directors** can fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders. Our charter documents also contain other provisions that could have an anti - takeover effect, including: ● only one of our three classes of directors will be elected each year; ● stockholders are not entitled to remove directors other than by a 66 2 / 3 % vote and only for cause; ● stockholders are not permitted to take actions by written consent; **41** ● stockholders cannot call a special meeting of stockholders; and ● stockholders must give advance notice to nominate directors or submit proposals for consideration at stockholder meetings. In addition, we are subject to the anti - takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock. Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment. You should not rely on an investment in our common stock to provide dividend income. We have not declared or paid cash dividends on our common stock to date and have no plans to pay cash dividends in the foreseeable future. ~~44We~~ **We** currently intend to retain our future earnings, if any, to fund the development and growth of our business. Investors seeking cash dividends should not purchase our common stock. Risks Related to the **Development and** Commercialization of Our Product CandidatesOLINVYK or any of our

~~other~~ product candidates for which we obtain approval may fail to achieve the degree of market acceptance by physicians, patients, third- party payors, and others in the medical community necessary for commercial success. OLINVYK or any of our ~~other~~ product candidates for which we obtain approval may fail to gain sufficient market acceptance by physicians, patients, third- party payors, and others in the medical community. If OLINVYK or our ~~other~~ product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not attain profitability. The degree of market acceptance of OLINVYK and our ~~other~~ product candidates for which we obtain approval will depend on a number of factors, including: ● the efficacy, safety, cost and potential advantages compared to alternative treatments; ● the timing of market introduction **,** ~~of the product candidate~~ as well as competitive products; ● our ability to offer the product for sale profitably and at competitive prices; ● the convenience and ease of administration compared to alternative treatments; ● the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; ● the strength of sales, marketing, and distribution support; ● the availability of third- party payor coverage and adequate reimbursement; ● the prevalence and severity of any side effects, including any limitations or warnings contained in a product' s approved labeling; ● publicity concerning our products or competing products and treatments; **42** ● FDA **' s, DEA** ' s and HHS' s policy initiatives regarding opioids, including enforcement focused on the inappropriate promotion and marketing of opioids; ● the public perception of opioids in general and the ongoing opioid crisis; ● the clinical indications for which the product is approved; and ● any restrictions on the use of our products, both on their own and together with other medications. We cannot assure you that OLINVYK or any product candidates for which we obtain regulatory approval in the future will achieve market acceptance among physicians, patients, patient advocacy groups, third- party payors or others in the medical community necessary for commercial success. Any failure by **OLINVYK or** our product candidates that obtain ~~45regulatory~~ -- **regulatory** approval to achieve market acceptance or commercial success could materially adversely affect our business, financial condition, results of operations and prospects. ~~If we are unable to maintain or expand our manufacturing, sales, marketing, and distribution capabilities or to enter into agreements with third parties to conduct these activities, we may not be successful in commercializing OLINVYK or any of our other product candidates if and when they are approved.~~ We ~~have implemented our sales and marketing infrastructure for the commercialization of OLINVYK, our first FDA- approved product. We currently do not expect to build sales, manufacturing and distribution capabilities outside of the United States, although this expectation could change in the future. There are substantial risks involved with establishing sales, marketing, and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercialization of OLINVYK is not successful or the commercial launch of another product candidate, if approved, is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred certain commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. There are a number of factors that may inhibit our efforts to successfully commercialize OLINVYK or any other drug products for which we receive marketing approval on our own, including: ● our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel or to outsource these tasks successfully to a third party; ● the inability of sales personnel to obtain access to physicians or other relevant personnel or educate adequate numbers of physicians or others on the benefit of our product candidates; ● the lack of complementary or other products to be offered by sales personnel, which may put us at a competitive disadvantage from the perspective of sales efficiency relative to companies with more extensive product lines; ● unforeseen costs and expenses associated with creating a sales and marketing organization; and ● efforts by our competitors to commercialize products at or about the time when our product candidates would be coming to market. As an alternative to establishing our own sales force, we may choose to partner with third parties that have well- established direct sales forces to sell, market and distribute our products. If we are unable to enter into collaborations with third parties for the commercialization of OLINVYK or any of our other drug candidates for which we obtain marketing approval, on acceptable terms or at all, or if any such partner does not devote sufficient resources to the commercialization of our product or otherwise fails in commercialization efforts, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval. For OLINVYK, we will need to partner with one or more third parties to sell, market and distribute this product, if approved, outside the United States. In April 2018 and May 2018, we entered into exclusive licensing agreements for the development and commercialization of OLINVYK in South Korea and China, respectively. Such partnerships in South Korea and China may not be successful, and we may be unsuccessful in our efforts to secure additional partnerships outside the United States. 46We~~ face substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than we do. OLINVYK is approved for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are not adequate. ~~We expect~~ OLINVYK ~~to compete~~ **competes** with generic IV opioid analgesics, such as morphine, hydromorphone and fentanyl. IV opioid analgesics are limited by well- known adverse side effects, such as respiratory depression, nausea, vomiting, constipation, and post- operative ileus, which can be exacerbated by the way these molecules are metabolized or cleared. OLINVYK ~~will also compete~~ **competes** against, or ~~be~~ **is** used in combination with, ~~OFIRMEV ® (~~IV acetaminophen ~~), marketed by Mallinckrodt plc~~ ; EXPAREL ® (liposomal bupivacaine), marketed by Pacira Pharmaceuticals, Inc.; ZYNRELEF ® (bupivacaine and meloxicam) marketed by Heron Therapeutics, Inc; CALDOLOR ® (IV ibuprofen), marketed by Cumberland Pharmaceuticals; DSUVIA ™ (sublingual sufentanil) marketed by ~~AcelRx~~ **Alora** Pharmaceuticals ~~, Inc.; and ANJESO ™ (IV meloxicam), marketed by Baudax Bio~~ , Inc.; XARACOLL ™ (bupivacaine HCL) implant, marketed by Innocoll Holdings plc; and POSIMIR ® (bupivacaine solution) marketed by **INNOCOLL Biotherapeutic** ~~DURECT Corporation.~~ . Together with generic versions of IV NSAIDs such as ketorolac and acetaminophen, and generic versions of local anesthetics such as bupivacaine, these non-opioid analgesics are currently used in combination with opioids in the multimodal management of moderate- to- severe acute pain. We also are aware of a number of products in mid- and late- stage clinical development that are aimed at improving the treatment of moderate- to- severe acute pain and may compete with OLINVYK. ~~AcelRx Pharmaceuticals, Inc. is developing~~

~~ZALVISO ™, a non- invasive PCA device containing sublingual sufentanil, which has received approval in the European Union.~~ Avenue Therapeutics, Inc. is developing an IV version of generic opioid tramadol for moderate- to- severe acute pain. Some of these potential competitive compounds are being developed by large, well- financed, and experienced pharmaceutical and biotechnology companies, or have been partnered with such companies, which may give them development, regulatory and marketing advantages over us. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for our product candidates, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third- party payors seeking to encourage the use of generic products or lower- cost branded products. Generic products are currently on the market for the OLINVYK indications and the indications that we are pursuing for our product candidates. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competing generic products. Some of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources, brand recognition and expertise than we do in research and development, manufacturing, nonclinical testing, conducting clinical trials, obtaining regulatory approvals, and selling and marketing approved products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early- stage companies ~~also~~ **43also** may prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. OLINVYK or any ~~other~~ product candidates for which we are able to obtain regulatory approval in the future may become subject to unfavorable pricing regulations, third- party payor coverage and reimbursement policies, or healthcare reform initiatives. Our ability to **sell OLINVYK or** commercialize ~~OLINVYK and~~ any of our **other** product candidates **, if approved,** successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available ~~47from~~ **from** government payor programs at the federal and state level, including Medicare and Medicaid, private health insurers, managed care plans and other organizations. Government authorities and other third- party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. In addition, for hospital products, a private health insurer or Medicare will typically reimburse a fixed fee for certain procedures, including in - patient surgeries. Pharmaceutical products such as OLINVYK that may be used in connection with the surgery generally will not be separately reimbursed and, therefore, a hospital would have to assess the cost of OLINVYK relative to its benefits. Current or future efforts to limit the level of reimbursement for in - patient hospital procedures could cause a hospital to decide not to use OLINVYK. A primary trend in the U. S. healthcare industry and elsewhere is cost containment. Government authorities and other third- party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications or procedures. Increasingly, third- party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement for a product or procedure may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any product candidate for which we or our collaborators obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to seek to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully **sell OLINVYK or** commercialize ~~OLINVYK or~~ any **of our other** product candidates for which marketing approval is obtained. The Inflation Reduction Act of 2022 contains substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U. S. Department of Health and Human Services that would require manufacturers to charge a negotiated " maximum fair price " for certain selected drugs or pay an excise tax for noncompliance, the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D to penalize price increases that outpace inflation, and requires manufacturers to provide discounts on Part D drugs. Substantial penalties can be assessed for noncompliance with the drug pricing provisions in the Inflation Reduction Act of 2022. The Inflation Reduction Act of 2022 could have the effect of reducing the prices we can charge and reimbursement we receive for our product and our product candidates, if approved, thereby reducing our profitability, and could have a material adverse effect on our financial condition, results of operations and growth prospects. The effect of Inflation Reduction Act of 2022 on our business and the pharmaceutical industry in general is not yet known. There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or analogous regulatory authorities outside the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution expenses. Interim reimbursement levels for new drugs, if applicable, also may not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently ~~restrict~~ **44restrict** imports of drugs from countries where they may be sold at lower prices than in the United States. Private third- party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our or

our collaborators' inability to promptly obtain coverage and adequate reimbursement rates from both government - funded and private payors for any approved drugs that we develop could adversely affect our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition. The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to ~~48continuing~~ -- **continuing** governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay commercial launch of the drug, possibly for lengthy time periods, and negatively impact our ability to generate revenue from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval. There can be no assurance that our product candidates, if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication, that they will be considered cost - effective by third- party payors, that coverage or an adequate level of reimbursement will be available, or that third- party payors' reimbursement policies will not adversely affect our ability to profitably sell our product candidates if they are approved for sale. Product liability lawsuits against us could cause us to incur substantial liabilities and limit **sales of OLINVYK or the development or** commercialization of ~~OLINVYK or~~ **our** ~~the development or commercialization of our other~~ product candidates. We face an inherent risk of product liability exposure as a result of the commercial sales of OLINVYK in the United States, the testing of our ~~other~~ product candidates in human clinical trials, and the commercialization of such ~~other~~ product candidates, if approved. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. For example, we may be sued if OLINVYK or any ~~other~~ product **candidate** we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability 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. If we cannot successfully defend ourselves against product liability claims, we will incur substantial liabilities or be required to limit commercialization of our products. Even a successful defense would require significant financial and management resources. Regardless of merit or eventual outcome, liability claims may result in: ● decreased demand for any product candidates or products that we may develop; ● injury to our reputation and significant negative media attention; ● withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs; ● initiation of investigations by regulatory agencies; ● significant costs to defend the related litigation; ● product recalls, withdrawals or labeling, marketing or promotional restrictions; ● substantial monetary awards to trial participants or patients; **45** ● loss of revenue; ● exhaustion of any available insurance and our capital resources; ● reduced resources of our management to pursue our business strategy; and ● the inability to commercialize any products that we may develop. We currently maintain product liability insurance coverage at levels which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance ~~coverage as we expand our commercialization 49efforts with respect to OLINVYK and~~ as we conduct additional clinical trials for our ~~other~~ product candidates. We will need to further increase our insurance coverage if we commence commercialization of any ~~additional~~ **of our** product candidates for which we obtain marketing approval. Insurance coverage is increasingly expensive, and in the future may be difficult to obtain for our ~~products~~ **product** and product candidates. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business, financial condition, results of operations and prospects. Concerns around the abuse of opioids, including law enforcement concerns over diversion of opioids and regulatory efforts to combat abuse, ~~could decrease the potential market for~~ **impact our ability to generate significant revenues from** OLINVYK **or any of our other product candidates** and may adversely impact external investor perceptions of our business. Prescription drug abuse and the diversion of opioids is a growing concern and has been referred to as an " opioid crisis " in the United States. Law enforcement and regulatory agencies **applied** ~~may apply~~ policies that seek to limit the availability or use of opioids. Such efforts may inhibit **sales of OLINVYK or** our ability to **successfully** commercialize our ~~products~~ **product candidates for which we obtain marketing approval**. Aggressive enforcement and unfavorable publicity regarding the use or misuse of opioids, including litigation or regulatory activity regarding sales or marketing of opioids, could have a material adverse effect on our business or reputation. Furthermore, a number of governmental entities have brought separate lawsuits against various pharmaceutical companies marketing and selling opioid pain medications, alleging misleading or otherwise improper promotion of opioid drugs to physicians and consumers. These efforts could reduce the potential size of the market for OLINVYK, decrease the revenues we are able to generate from its sale and adversely impact external investor perceptions of our business. Many state legislatures and the federal government have enacted legislation intended to reduce opioid abuse. In addition, the FDA, **DEA,** CDC and HHS each have initiatives to address opioid- related overdose, death and dependence. While these initiatives are generally focused on prescribing oral opioids in an outpatient settings, some of these initiatives, and any legislation or regulations resulting from these initiatives, may apply to all opioid drugs, including those like OLINVYK that are administered through an IV in a hospital setting. Many of these changes and others could cause us to expend additional resources in developing and commercializing our products to meet additional requirements. Risks Related to Regulatory Approval of Our Product CandidatesIf we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to timely commercialize, or to commercialize at all, our product candidates, and our ability to generate revenue will be materially

impaired. Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the European Medicines Agency and similar regulatory authorities outside the United States. Failure to obtain marketing approval for our product candidates will prevent us from commercializing these product candidates and will significantly limit our ability to generate revenue in the future. ~~We~~ **46We** have limited resources in filing and supporting the applications necessary to gain marketing approvals, and we have relied and expect to continue to rely on third parties 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 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. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product. The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take ~~50many~~ -- **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. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. OLINVYK has been classified as a Schedule II controlled substance under the Controlled Substances Act. The making, use, sale, importation, exportation and distribution of controlled substances are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies. We anticipate that TRV734, if approved, would also be classified as a Schedule II controlled substance under the Federal Controlled Substances Act of 1970. Controlled substances are subject to state, federal and foreign laws and regulations regarding their manufacture, use, sale, importation, exportation and distribution. Controlled substances are regulated under the Federal Controlled Substances Act of 1970, or CSA, and regulations of the DEA. The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse and no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. The FDA has designated OLINVYK ® (oliceridine) injection as a Schedule II controlled substance. Consequently, the manufacture, shipment, storage, sale, and use of OLINVYK will be subject to a high degree of regulation. Various states also independently regulate controlled substances. Though state- controlled substances laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule drugs as well. While some states automatically schedule a drug when the DEA does so, in other states there must be rulemaking or a legislative action. State scheduling may delay commercial sale of any controlled substance drug product for which we obtain federal regulatory approval and adverse scheduling could impair the commercial attractiveness of such product. We or our collaborators must also obtain separate state registrations in order to be able to obtain, handle and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions from the states in addition to those from the DEA or otherwise arising under federal law. For any of our products classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. There is a risk that DEA regulations may limit the supply of the compounds used in clinical trials for our product candidates and the ability to produce and distribute our products in the volume needed to both meet commercial demand and build inventory to mitigate possible supply disruptions. Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, recordkeeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of product ~~candidates~~ **47candidates** including controlled substances. The DEA, and some states, conduct periodic inspections of registered establishments that handle controlled substances. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of their restrictive nature, these regulations could limit commercialization of any of our product candidates that are classified as controlled substances. ~~51Failure~~ -- **Failure** to obtain marketing approval in international jurisdictions would prevent **OLINVYK or** our product candidates from being marketed abroad. To market and sell our products in the European Union, Asia, and many other jurisdictions, we, our current collaborators in South Korea and China for OLINVYK, or any future 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. 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 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, the failure to obtain approval in one jurisdiction 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. OLINVYK and any ~~other~~ product candidate for which we obtain marketing approval could be subject to post- marketing restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our ~~other products~~ **product candidates**, when and if any of them are approved. ~~Any~~ **OLINVYK and any** product candidate for which we obtain marketing approval, along with the manufacturing processes, post - approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post - marketing information and reports, registration, and listing requirements, current good manufacturing practice, or cGMP, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product. The FDA also may impose requirements for costly post - marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post - approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. However, companies may share truthful and not misleading information that is otherwise consistent with a product' s FDA approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off - label use and if we do not market our products for only their approved indications, we may be subject to enforcement action for off - label marketing. Violations of the Federal Food, Drug, and Cosmetic 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. Even though the FDA has granted approval of OLINVYK, the scope and terms of the approval may limit **the** ~~our ability to commercialize OLINVYK and, therefore, our~~ ability to generate substantial sales revenues **from OLINVYK either on our own or with a partner**. The FDA has approved OLINVYK only for use in adults for the management of acute pain severe enough to require an intravenous ~~opioid~~ **48opioid** analgesic and for whom alternative treatments are inadequate. The label for OLINVYK also contains a " boxed " warning about addiction, abuse, misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, and risks from concomitant use with benzodiazepines or other central nervous system depressants. This " boxed " warning may discourage physicians from prescribing OLINVYK to patients. ~~52In~~ **In** addition, later discovery of previously unknown adverse events or other problems with OLINVYK or our other product candidates, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including: ● the need to generate additional clinical data in order to provide information to the FDA to sufficiently address any future concerns for OLINVYK or ~~other~~ **our** product candidates for which we may obtain regulatory approval; ● restrictions on such products, 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 letters, untitled letters, or Form 483s; ● withdrawal of the products from the market; ● refusal to approve pending applications or supplements to approved applications that we submit; ● recall of products; ● fines, restitution or disgorgement of profits or revenue; ● suspension or withdrawal of marketing approvals; ● refusal to permit the import or export of our products; ● product seizure; or ● injunctions or the imposition of civil or criminal penalties. If any of these actions were to occur, we may have to discontinue commercializing OLINVYK, limit our sales and marketing efforts, conduct further post- approval studies, and / or discontinue or change any other ongoing or planned clinical studies, which in turn could result in significant expense and delay or limit our ability to generate sales revenues. Moreover, the FDA' s policies may change and additional government regulations may be enacted that could impose additional post- marketing obligations on any approved products. 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 obtained. ~~Risks~~ **49Risks** Related to the Discovery and Development of Our Product CandidatesWe have only one product ~~candidate~~, OLINVYK, for which we received marketing approval from the FDA. If we are unable to ~~successfully~~ **find a** ~~commercialize~~ --- **commercial partner** ~~or~~ **for** ~~achieve market acceptance of~~ OLINVYK, or if we are unable to complete development of our ~~other~~ product candidates, or if we experience significant delays in doing so, our business will be materially harmed. We have only one product, OLINVYK, for which we have received marketing approval by the FDA. To this point, we have invested substantially all of our efforts and financial resources in the identification and development of biased ligands. Our ability to generate product revenue ~~will~~ **may** depend heavily on the successful ~~commercialization and market acceptance~~ **ability to find a commercial partner** of OLINVYK and the development and commercialization, if approved, of our other product ~~53candidates~~ -- **candidates**. The success of OLINVYK and our development- stage product candidates will depend on several factors, including the following: ● successful completion of nonclinical studies and clinical trials; ● receipt of marketing approvals from applicable regulatory authorities; ● obtaining, maintaining, and protecting our intellectual property portfolio, including patents and trade secrets, and regulatory exclusivity for our product candidates; ● making arrangements with third- party manufacturers for, or establishing, commercial manufacturing capabilities; ● ~~deploying our direct sales force and establishing market acceptance of OLINVYK;~~ ● launching commercial sales of our ~~other~~ product candidates, if and when approved, whether alone or in collaboration with others; ● acceptance of our ~~other~~ product candidates, if and when approved, by patients, the medical community, and third-party payors; ● effectively competing with other therapies; ● obtaining and maintaining healthcare coverage of our products and adequate reimbursement; and ● maintaining a continued acceptable safety profile of our products following 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 inability to

successfully commercialize our product candidates, if approved, which would materially harm our business. Nonclinical and clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates. Clinical testing is expensive, can take many years to complete, and has a high risk of failure. It is impossible to predict when or if any of our ~~additional~~ product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete nonclinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. A failure of one or more clinical trials can occur at any stage of testing. The outcome of nonclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim or topline results of a clinical trial do not necessarily predict final results. Moreover, nonclinical and clinical data often are susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. We may experience numerous unforeseen events during, or as a result of, clinical trials, which could ~~delay~~ **50delay** or prevent our ability to receive marketing approval or subsequently to commercialize our product candidates, including: ● regulatory agencies or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at prospective trial sites; ● we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites; ~~54~~ ● clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulatory agencies may require us, to conduct additional clinical trials 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 participants may drop out of these clinical trials 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, or at all; ● we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks; ● regulatory agencies or institutional review boards 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; ● the cost of clinical trials of our product candidates may be greater than we anticipate; ● 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; and ● our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulatory agencies or institutional review boards to suspend or terminate the trials. 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 complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may: ● be delayed in obtaining marketing approval for our product candidates; ● not obtain marketing approval at all; ● obtain approval for 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; ● be subject to additional post - marketing testing and / or reporting requirements; or ● have the product removed from the market after obtaining marketing approval. ~~Our~~ **51Our** product development costs also will increase if we experience delays in testing or in receiving marketing approvals. We do not know whether any of our nonclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant nonclinical study 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, thereby harming our business and results of operations. ~~55We~~ **We** may be unable to obtain regulatory approval for our product candidates under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of our product candidates and adversely impact our potential to generate revenue, our business and our results of operations. The research, testing, manufacturing, labeling, licensure, sale, marketing and distribution of biopharmaceutical products are subject to extensive regulation by the FDA and comparable regulatory authorities in the United States and other countries, and such regulations differ from country to country. We are not permitted to market our product candidates in any jurisdiction until they receive the requisite marketing approval from the applicable regulatory authorities of such jurisdictions. To gain approval to market our product candidates, we must provide the FDA and foreign regulatory authorities with nonclinical and clinical data that adequately demonstrate the safety and efficacy of the product for the intended indication applied for in the applicable regulatory filing. The approval process is typically lengthy and expensive, and approval is never certain. Our receipt of regulatory approval in the United States for OLINVYK does not mean that we will be successful in obtaining regulatory approval for our other product candidates ~~or obtaining approval for OLINVYK in other countries~~. The FDA or any foreign regulatory authorities can delay, limit or deny approval of our product candidates for many reasons, including: ● the FDA or other equivalent foreign regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials; ● our inability to demonstrate to the satisfaction of the FDA or the equivalent foreign regulatory authority that any of our product candidates is safe and effective for the requested indication; ● the results of our clinical trials may not meet the level of statistical significance or clinical meaningfulness required by the FDA or other equivalent foreign regulatory authorities for marketing approval; ● the FDA or other equivalent foreign regulatory authorities may not accept data generated from our clinical trial sites; ● the FDA or other equivalent foreign regulatory authorities may find the chemistry, manufacturing and controls data insufficient to support the quality of our product candidates; ● the FDA or other equivalent foreign regulatory authorities may identify deficiencies in the manufacturing processes or facilities of our CDMOs; ● the FDA or equivalent foreign regulatory authorities may not approve the formulation, dosing, labeling or specifications; or ● the potential for approval policies or regulations of the FDA or the

equivalent foreign regulatory authorities to significantly change in a manner rendering our clinical data insufficient for approval. Any of these factors, many of which are beyond our control, may result in our failing to obtain regulatory approval to market any of our ~~other~~ product candidates ~~or approval of OLINVYK in foreign countries~~, which could materially adversely affect our business, financial condition, results of operations and prospects. ~~If~~ **52If** we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented. We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our ~~56clinical~~ -- **clinical** trials may instead enroll in clinical trials of our competitors ~~'~~ **'** product candidates. Patient enrollment is affected by other factors including: ● the severity of the disease under investigation; ● our ability to recruit clinical trial investigators with appropriate competencies and experience; ● the eligibility criteria for the study in question; ● the size of the patient population required for analysis of the trial' s primary endpoints; ● the perceived risks and benefits of the product candidate under study; ● availability and efficacy of approved medications for the disease under investigation; ● the efforts to facilitate timely enrollment in clinical trials; ● the patient referral practices of physicians; ● the ability to monitor patients adequately during and after treatment; and ● the proximity and availability of clinical trial sites for prospective patients. These factors can be exacerbated by other situations, such as **our** ~~the COVID- 19 pandemic and the efforts to mitigate it. Our~~ inability to enroll a sufficient number of patients for our clinical trials **which** would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. If serious adverse or unacceptable side effects are identified during the development of our product candidates or following their approval by the FDA or foreign regulatory authorities, we may need to abandon or limit our development of some of our product candidates, limit the commercial profile of an approved label, or it may result in significant negative consequences following marketing approval, if any. If our product candidates are associated with adverse side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the side effects or other characteristics are less prevalent, less severe, or more acceptable from a risk- benefit perspective. In our industry, many compounds that initially showed promise in early- stage testing have later been found to cause side effects that prevented further development of the compound or significantly limited its commercial opportunity. OLINVYK and TRV734 are both biased ligands targeted at the MOR. Common adverse reactions for agonists of the MOR include respiratory depression, constipation, nausea, vomiting, and addiction. In rare cases, MOR agonists can cause respiratory arrest requiring immediate medical intervention. The label for OLINVYK contains a " boxed " warning about addiction, abuse, misuse, life- threatening respiratory depression, neonatal opioid withdrawal syndrome, ~~and~~ **53and** risks from concomitant use with benzodiazepines or other central nervous system depressants. This " boxed " warning may discourage physicians from prescribing OLINVYK to patients. If our clinical trials reveal a high and unacceptable severity and prevalence of side effects, these trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development or deny approval of our product candidates for any or all targeted indications. Drug related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial and could result in potential product liability claims. ~~57Additionally~~ -- **Additionally** , if we or others later identify undesirable side effects caused by OLINVYK or one or more of our ~~other~~ product candidates for which we may obtain marketing approval, a number of potentially significant negative consequences could result, including: ● regulatory authorities may require additional warnings on the label or even withdraw approvals of such product; ● we may be required to recall a product or change the way such product is administered to patients; ● regulatory authorities may require additional warnings on the label, such as a " black box " warning or a contraindication, or issue safety alerts, press releases or other communications containing warnings or other safety information about the product; ● we may be required to implement a REMS, or create a medication guide outlining the risks of such side effects for distribution to patients, if one is not required in connection with regulatory approval; ● additional restrictions may be imposed on the marketing or promotion of the particular product or the manufacturing processes for the product or any component thereof; ● we could be sued and held liable for harm caused to patients; and ● our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects. We may not be successful in our efforts to expand our pipeline of product candidates. One element of our strategy has been to expand our pipeline of therapeutics based on biased ligands and advance these product candidates through clinical development for the treatment of a variety of indications. Although we continue to assess the future development of our pipeline, without internal discovery research capabilities, we will need to expand our pipeline through other means, including, for example, by in- licensing product candidates for further development. We may not be able to identify, acquire, and develop product candidates that are safe and effective. Even if we are successful in continuing to expand our pipeline, the potential product candidates that we identify or in- license may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. If we do not successfully develop **, receive regulatory approval** and commercialize product candidates, we will not be able to obtain product revenue in future periods, which would make it unlikely that we would ever achieve profitability. We may expend our limited resources to pursue a particular product candidate or indication and thereby fail to capitalize on other product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with ~~other~~ **54other** product candidates that later prove to have fewer clinical or regulatory risks and / or greater commercial

potential. 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 and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. ~~58In~~ **In** the future, we may conduct a substantial portion of the clinical trials for our product candidates outside of the United States and, if approved, we may seek to market our product candidates abroad through third- party collaborators. Accordingly, we will be subject to the risks of doing business outside of the United States. In the future, we may conduct a substantial portion of our clinical trials outside of the United States and we may seek to market **our** ~~OLIVNYK and any other~~ product candidates for which we obtain approval outside of the United States. We are thus subject to risks associated with doing business outside of the United States. **We** ~~With respect to OLIVNYK and our other product candidates, we~~ may choose to partner with third parties that have direct sales forces and established distribution systems, in lieu of our own sales force and distribution systems, which would indirectly expose us to these risks. Our business and financial results in the future could be adversely affected due to a variety of factors associated with conducting development and marketing of our product candidates, if approved, outside of the United States, including: ● efforts to develop an international sales, marketing and distribution organization may increase our expenses, divert our management' s attention from the development of product candidates or cause us to forgo other profitable licensing opportunities in these geographies; ● changes in a specific country' s or region' s political and cultural climate or economic condition; ● unexpected changes in foreign laws and regulatory requirements; ● difficulty of effective enforcement of contractual provisions in local jurisdictions; ● inadequate intellectual property protection in foreign countries; ● differing payor reimbursement regimes, governmental payors or patient self- pay systems and price controls; ● trade protection measures, import or export licensing requirements such as Export Administration Regulations promulgated by the U. S. Department of Commerce and fines, penalties or suspension or revocation of export privileges; ● regulations under the U. S. Foreign Corrupt Practices Act and similar foreign anti- corruption laws; ● the effects of applicable foreign tax structures and potentially adverse tax consequences; and ● significant adverse changes in foreign currency exchange rates which could make the cost of our clinical trials, to the extent conducted outside of the United States, more expensive. Risks Related to Our Dependence on Third PartiesOur current collaborators are, and any future relationships or collaborations we may enter into may be, important to us. If we are unable to maintain our relationship with any of these collaborations, or if our relationship with these collaborators is not successful, our business could be adversely affected. We have limited capabilities for product development, sales, marketing, and distribution. As a result, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and potential ~~commercialization~~ **55commercialization** of ~~these~~ **our product** candidates ~~or for the commercialization of OLINVYK in certain territories outside of the United States, if approved in those jurisdictions~~. For example, we entered into license agreements with partners in South Korea and China in 2018 whereby these parties will develop, seek regulatory approval for, and, if successful, commercialize OLINVYK. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator' s evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on ~~59acceptable~~ -- **acceptable** terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, 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 product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected. Any future collaborations we might enter into with third parties, may pose a number of risks, including the following: ● collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations; ● collaborators may not perform their obligations as expected; ● collaborators may elect not to continue development or commercialization programs or may not pursue commercialization of any product candidates that achieve regulatory approval based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities; ● collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing; ● collaborators could fail to make timely regulatory submissions for a product candidate; ● collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements; ● collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; ● product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to limit or eliminate efforts and resources to the commercialization of our product candidates; ● a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products; ● disagreements with collaborators, including disagreements over proprietary rights, contract interpretation, or the preferred course of development, might cause delays or termination of the research, development or ~~commercialization~~ **56commercialization** of product candidates, might lead to

additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time- consuming and expensive; ● collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; ~~60~~ ● collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; ● collaborations may be terminated at the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates; and ● collaborators may be affected by political instability or instability from a regional or global pandemic disease, such as the recent coronavirus outbreak. If any collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product platform and product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. The risks relating to our product development, regulatory approval and commercialization described in this Annual Report also apply to the activities of our therapeutic program collaborators. If a future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected. We rely, and expect to continue to rely, on third parties to conduct our nonclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or complying with applicable regulatory requirements. We rely on third parties, such as contract research organizations, clinical research organizations, clinical data management organizations, medical institutions, and clinical investigators to conduct our nonclinical studies and clinical trials for our product candidates. The agreements with these third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that could delay our product development activities. Some of these third parties may experience shutdowns or other disruptions **due to future** ~~as a result of the COVID- 19 pandemic~~ **pandemics** , including, but not limited to, the ability to adequately staff a project or effectively and expeditiously enroll patients in a clinical study, and therefore may be unable to provide the level of service that we received in the past. 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 nonclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our nonclinical studies are conducted in accordance with GLP, as appropriate. Moreover, the FDA requires us to comply with standards, commonly referred to as GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators, and trial sites. If we or any of our clinical research organizations fail to comply with applicable GCPs, 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 regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our ~~clinical~~ **57clinical** trials must be conducted with product 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. We also are required to register certain clinical trials and post the results of these clinical trials when completed on a government- sponsored public database, ClinicalTrials. gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. ~~61The~~ -- **The** third parties with whom we have contracted to help perform our nonclinical studies or clinical trials also may 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 nonclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. If any of our relationships with these third- party contract research organizations or clinical research organizations terminate, we may not be able to enter into arrangements with alternative contract research organizations or clinical research organizations or to do so on commercially reasonable terms. Switching or adding additional contract research organizations or clinical research organizations involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new contract research organization or clinical research organization commences work. As a result, delays could occur that could compromise our ability to meet our desired development timelines. Although we seek to carefully manage our relationships with our contract research organizations and clinical research organizations, there can be no assurance that we will not encounter similar challenges or delays in the future. We contract with third parties for the manufacture of commercial supply of OLINVYK and for clinical and nonclinical supply of our ~~other~~ product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of OLINVYK or our ~~other~~ product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts. We have no internal manufacturing capabilities and do not have any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of commercial supply of OLINVYK and the manufacture of supply of our ~~other~~ product candidates for nonclinical and clinical testing, as well as for commercial manufacture, if any of such ~~other~~ product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of OLINVYK or our ~~other~~ product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. We also expect to rely on third-

party manufacturers or third- party collaborators for the manufacture of commercial supply of any other product candidates for which our collaborators or we obtain marketing approval. We may be unable to establish any agreements with third- party manufacturers or to do so on acceptable terms. Our reliance on third- party manufacturers for commercial supply of OLINVYK and for any additional product candidates for which we obtain regulatory approval entails additional risks, including: ● reliance on the third party for regulatory compliance and quality assurance; ● the possible breach of the manufacturing agreement by the third party; ● limitations on supply availability resulting from capacity and scheduling constraints of the third parties; ● manufacturing delays if our third- party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us; ● the possible misappropriation of our proprietary information, including our trade secrets and know- how; **58** ● impact on our reputation in the marketplace if manufacturers of our products, once commercialized, fail to meet the demands of our customers; and ● the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us. ~~62The~~ -- **The** failure of any of our contract manufacturers to maintain high manufacturing standards could result in injury or death of clinical trial participants or patients using products. Such failure could also result in product liability claims, product recalls, product seizures or withdrawals, delays or failures in testing or delivery, cost overruns or other problems that could seriously harm our business or profitability. The facilities used by our contract manufacturers to manufacture our product candidates (and commercial supply of those product candidates, if approved) must be approved by the FDA pursuant to inspections that will be conducted after we submit an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with current cGMP regulations for manufacture of our product candidates. These regulations cover all aspects of the manufacturing, testing, quality control and recordkeeping relating to our product candidates and any products that we may commercialize. Third- party manufacturers may not be able to comply with the cGMP regulations or similar regulatory requirements outside the United States. 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 or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products. OLINVYK and **any** ~~our other~~ product candidates that we may commercialize, if approved, 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. 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 second source for bulk drug substance or drug product. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. We may incur added costs and delays in identifying ~~and~~ **,** qualifying **, and obtaining applicable regulatory approval (s) of** any replacement manufacturers. The DEA restricts the importation of a controlled substance finished drug product when the same substance is commercially available in the United States, which could reduce the number of potential alternative manufacturers for OLINVYK or our other MOR targeted product candidates. In addition, a DEA quota system controls and limits the availability and production of controlled substances and the DEA also has authority to grant or deny requests for quota of controlled substances, which includes the active ingredient in OLINVYK. Supply disruptions could result from delays in obtaining DEA approvals for controlled substances or from the receipt of quota of controlled substances that are insufficient to meet future product demand. The quota system also may limit our ability to build inventory as a method for mitigating possible supply disruptions of OLINVYK. Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis. 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 products, producing additional losses and depriving us of potential product revenue.

59Our business could be impacted by sanctions imposed on WuXiCertain U. S. lawmakers have encouraged sanctions and introduced legislation that could affect WuXi AppTec (Hong Kong) Limited (" WuXi Apptec "), and WuXi Apptec' s affiliate XenoBiotics Laboratories, Inc. (" XenoBiotics, " together with WuXi Apptec " Wuxi ") and companies that do business with WuXi. WuXi is our primary manufacturer and supplier of an important starting material for the active pharmaceutical ingredient for OLINVYK. WuXi is also in the process of running certain toxicology and bioanalytic studies associated with TRV045. We, and the pharmaceutical industry generally, depend on China- based partners such as WuXi for integral chemical synthesis, reagents, starting materials, and ingredients. Sanctions against WuXi, and the impact that such sanctions could have on its business, could negatively impact our ability to manufacture the starting material for the active pharmaceutical ingredient for OLINVYK and could cause delays, disruptions and cost increases to our toxicology and bioanalytic studies for TRV045. Materials necessary to manufacture our product or product candidates may not be available on commercially reasonable terms, or at all, which may delay the development and commercialization of our product or product candidates. We currently rely on the manufacturers of our product and product candidates to purchase from third- party suppliers the materials necessary to produce the compounds for our nonclinical studies and clinical trials, and we rely, or will rely, on these other manufacturers for commercial distribution of **our** ~~OLINVYK and any other products~~ **product candidates** for which we may obtain regulatory approval. Suppliers may not sell these materials to our manufacturers at the time we need them or on commercially reasonable terms and all such prices are susceptible to fluctuations in price and availability due to transportation costs, government regulations, price controls and changes in economic climate or other foreseen circumstances. We do not have any control over the process or timing of the acquisition of these materials by our ~~63manufacturers~~ -- **manufacturers** . We may enter into agreements to purchase certain materials and provide them to our manufacturers, with all the risks and uncertainties of supply associated with those purchases. If we or our manufacturers are

unable to obtain these materials for our nonclinical studies and clinical trials, product testing and potential regulatory approval of our product candidates would be delayed, significantly impacting our ability to develop and commercialize our product candidates. If our manufacturers or we are unable to purchase these materials for commercial distribution of our product or, after regulatory approval has been obtained, our product candidates, the commercial launch of our product and product candidates, if approved, would be delayed or there would be a shortage in supply, which would materially affect our ability to generate revenues from the sale of our product or product candidates. We rely on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable. As part of our strategy to mitigate development risk, we seek to develop product candidates with validated mechanisms of action and we utilize biomarkers to assess potential clinical efficacy early in the development process. This strategy necessarily relies upon clinical data and other results obtained by third parties that may ultimately prove to be inaccurate or unreliable. Further, such clinical data and results may be based on products or product candidates that are significantly different from our product candidates. If the third- party data and results we rely upon prove to be inaccurate, unreliable or not applicable to our product candidates, we could make inaccurate assumptions and conclusions about our product candidates and our research and development efforts could be compromised. Risks Related to Our Intellectual PropertyIf we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired. Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates. ~~The~~ **60The** patent prosecution process is expensive and time- consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Should we enter into collaborations with third parties, we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. 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. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. 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 a first filing, or in some cases 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. 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 which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The Leahy- Smith America Invents Act, or the Leahy- Smith Act, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On ~~64September~~ -- **September** 16, 2011, the Leahy- Smith Act was signed into law. The Leahy- Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent and Trademark Office continues to develop and implement new regulations and procedures to govern administration of the Leahy- Smith Act, and many of the substantive changes to patent law associated with the Leahy- Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy- Smith Act will have on the operation of our business. However, 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 and financial condition. Moreover, we may be subject to a third- party preissuance submission of prior art to the United States Patent and Trademark Office, 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, render unenforceable, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products 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 patent applications issue as patents, they may not issue in a form that 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 our owned or licensed patents by developing similar or alternative technologies or products in a non- infringing manner. The issuance of a patent does not foreclose challenges to its inventorship, scope, validity or enforceability. Therefore, 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 freedom to operate 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 products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new ~~product~~ **61product** 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. We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful. Competitors may infringe our issued patents 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 that we infringe their patents. In addition, in a patent infringement proceeding, 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. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, rendered unenforceable, or interpreted narrowly. We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms. A third party may hold intellectual property, including patent rights that are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. ~~65Third~~ -- **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, market and sell our 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 products and technology, including interference or derivation proceedings before the United States Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. 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 products 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 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 or trade secrets of third parties could have a similar negative impact on our business. If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business. We are currently party to license agreements for technologies that we use in conducting our drug discovery activities. In the future, we may become party to licenses that are important for product development and commercialization. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product or utilize any technology that is covered by these agreements or may face other ~~penalties~~ **62penalties** under the agreements. Such an occurrence could materially and adversely affect the value of a product candidate being developed under any such agreement or could restrict our drug discovery activities. Termination of these agreements or reduction or elimination of our rights under these 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 or technology. 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. ~~66If~~ **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. Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their

greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace. If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed. In addition to seeking patent protection for our product candidates, we rely on trade secrets, including unpatented know- how, technology and other proprietary information, to maintain our competitive position. We limit disclosure of such trade secrets where possible, but we also seek to protect these trade secrets, in part, by entering into non - disclosure and confidentiality agreements with parties who do have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time - consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently ~~developed~~ **63developed** by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed. Risks Related to Legal Compliance MattersOur current and future relationships with customers and third- party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti - kickback, fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings. Healthcare providers, physicians and third- party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of OLINVYK and any other product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third- party payors, and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti - Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which we conduct research, sell, market, and distribute OLINVYK and any other drugs for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U. S. federal and state governments and by governments in foreign jurisdictions in which we ~~67conduct~~ -- **conduct** our business. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include: ● the federal Anti- Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs, such as Medicare and Medicaid; ● federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act which can be enforced by individuals, on behalf of the government, through civil whistleblower or qui tam actions, and civil monetary penalty laws prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; ● the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes, among other things, criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; ● HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose, among other things, obligations on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information; ● the federal Physician Payments Sunshine Act, also known as Open Payments program, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to " payments or other transfers of value " made to physicians, which is defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and teaching hospitals and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their ~~immediate~~ **64immediate** family members. Beginning in 2022, applicable manufacturers are also required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse- midwives; and ● the Foreign Corrupt Practices Act, or FCPA, which prohibits any U. S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business; and ● analogous state and foreign laws and regulations, such as state anti- kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures, or drug pricing; state and local laws that require the registration of pharmaceutical sales representatives; and state and foreign laws, such

as the General Data Protection Regulation (EU) 2016 / 679, governing the privacy and security of health information in certain circumstances, many of which ~~68differ~~ **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 may 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, including, without limitation, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations to resolve allegations of non- compliance with these laws, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to significant criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which also could materially affect our business. Healthcare reform measures may increase the difficulty and cost for us to successfully commercialize our product and product candidates, if approved, and affect the prices we may obtain. The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could restrict or regulate post- approval activities relating to our product and product candidates, if approved, including implementing cost- containment programs to limit the growth of government- paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. The Affordable Care Act was 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. ~~Among~~ **65Among** the provisions of the Affordable Care Act that have been implemented since enactment and are of importance to the successful commercialization of a pharmaceutical product are the following: ● an annual, nondeductible fee on any entity that manufactures, or imports specified branded prescription drugs or biologic agents; ● an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program; ● expansion of healthcare fraud and abuse laws, including the U. S. civil False Claims Act and the Anti- Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance; ● a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50 % point- of- sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer' s outpatient drugs to be covered under Medicare Part D; ● extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; ● a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected; ● expansion of eligibility criteria for Medicaid programs; ~~69~~ ● expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; ● requirements to report certain financial arrangements with physicians and teaching hospitals; ● a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to physicians; and ● a new Patient- Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. There have been significant ongoing judicial, administrative, executive and legislative efforts to modify or eliminate the Affordable Care Act. For example, the Tax Act enacted on December 22, 2017, repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code, commonly referred to as the individual mandate. Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $ 1. 2 trillion for the fiscal years 2012 through 2021, triggering the legislation' s automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2. 0 % per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2 % reduction, on average, to 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief and Economic Security Act, or the CARES Act, which was designed to provide financial support and resources to individuals and businesses affected by the COVID- 19 pandemic, suspended the 2 % Medicare sequester from May 1, 2020 to March 31, 2022. As of July 2, 2022, the 2 % sequester resumed. The sequester will remain in place through 2030. On January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. ~~The~~ **66The** Affordable Care Act has also been subject to challenges in the courts. On December 14, 2018, a Texas U. S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the " individual mandate " was repealed by Congress. On December 18, 2019, the Fifth Circuit U. S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the Texas District Court to reconsider its earlier invalidation of the entire Affordable Care Act. On June 17, 2021, the Supreme Court ruled that the plaintiffs lacked standing to challenge the law as they had not alleged personal injury traceable to the allegedly unlawful conduct. As a result, the Supreme Court did not rule on the constitutionality of the ACA or any of its provisions. Further changes to and under the Affordable Care Act remain possible but it is unknown what form any such changes or any law proposed to replace or revise the Affordable Care Act would take, and how or whether it may affect our business in the future. We expect that changes to the Affordable Care Act, the Medicare and Medicaid programs, changes allowing the federal government to directly negotiate drug prices and changes stemming from

other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry. We expect that the Affordable Care Act, as well as other healthcare reform measures that have and 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 our product and product candidates, if approved, and could seriously harm our future revenues. Any reduction in reimbursement from Medicare, Medicaid, or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or successfully commercialize our product and product candidates, if approved. ~~70Governments~~ -- **Governments** outside the United States tend to impose strict price controls, which may adversely affect our revenue, if any. In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and 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. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially. 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 to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. In addition, we may incur substantial costs in order to comply with current or future environmental, health, and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties, or other sanctions. ~~Risks~~ **67Risks** Related to Employee Matters and Managing Our GrowthOur future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel. We are highly dependent on the development, clinical, business development, legal, financial, and commercial expertise of our executive officers. Although we have entered into employment agreements with these individuals, each of them 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 and retaining qualified management, scientific, clinical, manufacturing, sales and marketing, and other personnel also will be critical to our success. The loss of the services of our executive officers or other key employees or consultants could impede the achievement of our development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees or consultants 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, gain regulatory approval of and commercialize products. 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, clinical, and commercial advisors, to ~~71assist~~ -- **assist** us in formulating our development and commercialization strategy. Our consultants and advisors 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. In the future, we may expand our development, regulatory, manufacturing, sales, marketing, and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. In the future, we may experience growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, manufacturing, sales, marketing, and distribution. To manage potential future growth, we may be required to implement and improve our managerial, operational and financial systems, expand our facilities and recruit and train additional qualified personnel. Due to our limited financial resources, 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. Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could expose us to liability and hurt our reputation. We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct also could involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or

lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including the imposition of significant civil, criminal and administrative penalties, including, without limitation, damages, fines, disgorgement, imprisonment, exclusion from participation in government ~~healthcare~~ **68healthcare** programs, such as Medicare and Medicaid, integrity oversight and reporting obligations to resolve allegations of non- compliance with these laws, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. General Risk ~~FactorsRaising~~ **Factors 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 revenue and positive cash flows from operations, we expect to finance our cash needs through a combination of equity offerings, debt financings, and license and development agreements in connection with any collaborations. 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, your ownership interest will be diluted, either at the time of such capital raise or thereafter, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Preferred equity financing and additional debt 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, or that include covenants requiring us to meet certain obligations, such as minimum cash requirements or net revenue targets. 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, ~~72research~~ -- **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 when needed, we may be required to delay, limit, reduce, or terminate our product development or our current or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. An active trading market for our common stock may not continue to develop or be sustained. Although our common stock is listed on the Nasdaq, we cannot assure you that an active, liquid trading market for our shares will continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for you to sell shares quickly or without depressing the market price for the shares or to sell your shares at all. If equity research analysts do not continue to publish research or reports or publish unfavorable research or reports about us, our business or our industry, 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. We have only limited research coverage by equity research analysts. Equity research analysts may elect not to initiate or continue to provide research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. We have no control over the analysts or the content and opinions included in their reports. The price of our 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 our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline. Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business, cash flow, financial condition or results of operations. 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 operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Act enacted many significant changes to the U. S. tax laws. Future guidance from the Internal Revenue Service and other ~~tax~~ **69tax** authorities with respect to the Tax Act may affect us, and certain aspects of the Tax Act could be repealed or modified in future legislation. In addition, it is uncertain if and to what extent various states will conform to the Tax Act or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one- time charges, and could increase our future U. S. tax expense. If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired. We are subject to the reporting requirements of the Exchange Act, the Sarbanes- Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, and the rules and regulations of Nasdaq. The Sarbanes - Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal controls over financial reporting. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. For our fiscal year ended December 31, ~~2021~~ **2023** , we are obligated to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Annual Report on Form 10- K filing for that year, as required by Section 404 (a) of the Sarbanes- Oxley Act. ~~73~~ **We incur costs and demands upon management as a result of being a public company. As a public company listed in the United States, we are incurring, and will continue to incur, significant legal, accounting and other costs. These costs could negatively affect our financial results. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the SEC and stock exchanges, may increase legal and financial compliance costs and make some activities more time consuming. These laws, regulations and standards are subject to varying interpretations and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management' s time and attention from revenue - generating activities to compliance activities. If, notwithstanding our efforts to comply with new laws,**

regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed. Failure to comply with these rules also might make it more difficult for us to obtain some types of insurance, including directors' and officers' liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our Board of Directors, on committees of our Board of Directors or as members of senior management. Our business and operations would suffer in the event of system failures. We utilize information technology systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data. There can be no assurance that we will be successful in preventing cyber- attacks or successfully mitigating their effects. Despite our implementation of security measures, our internal computer systems and operations and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, outbreak of regional or global pandemic diseases, such as the recent coronavirus outbreak, terrorism, war, and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption to our product candidate development programs. For example, the loss of data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a 70