Risk Factors Comparison 2024-03-28 to 2023-03-08 Form: 10-K

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

In addition to the other information in this Annual Report on Form 10- K, a number of factors may affect our business and prospects. These factors include but are not limited to the following, which you should consider carefully in evaluating our business and prospects. If any of the following risks actually occur, our business, financial condition, results of operations and growth prospects may be materially and adversely affected. Summary • We are dependent on the success of larsucosterol and the path to regulatory approval is uncertain; we cannot be certain that it will receive regulatory approval or be commercialized • **The FDA or other regulatory agencies may require more information or clinical studies for our product candidates, and our product candidates may never be approved •** We will require, and may have difficulty or be unsuccessful in raising needed capital in the future to continue to operate as a going concern **• We contract with third parties for the manufacture of larsucosterol and expect to continue to do so for any required additional clinical trials as well as the commercialization of larsucosterol. Our reliance on third parties increases the risk that submissions for regulatory approval of larsucosterol may be delayed or that we will not have sufficient quantities of larsucosterol available at an acceptable cost, which could delay, prevent or impair our development and commercialization efforts of larsucosterol • Safety data and indications of activity from completed Phase 1 and 2 clinical trials of larsucosterol may not predict safety, activity or therapeutic efficacy in future trials • Future clinical trials for larsucosterol may be delayed and may not demonstrate efficacy or safety** • The FDA' s Fast Track Designation of larsucosterol ~~in AH~~ may not lead to a faster development or regulatory review or approval ~~• Safety data and indications of activity from completed larsucosterol clinical trials may not predict safety, activity or efficacy in future trials~~ • Open- label trials of larsucosterol in **MASH and** AH ~~and NASH~~ have inherent limitations ~~• Ongoing and future clinical trials for larsucosterol may be delayed and may not demonstrate efficacy or safety~~ • We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates • Key components of larsucosterol are provided by a limited number of suppliers, and supply shortages or loss of these suppliers could result in delays or interruptions in supply or increased costs • Macroeconomic uncertainties have in the past impacted and may continue to adversely impact our business, including posing challenges to conducting clinical trials • We have a significant amount of debt. Compliance with repayment obligations and other covenants may be difficult; failure to fulfill our obligations may cause the repayment obligations to accelerate • We do not control the commercialization of POSIMIR, PERSERIS or Methydur • For certain of our product candidates, we depend to a large extent on third- party collaborators, and we have limited or no control over their development, sales, distribution, disclosure, regulatory strategy or potential commercialization • **Our business strategy includes relying on third parties to support development, clinical trials, manufacturing and commercialization of product candidates •** Cancellation of third- party collaborations may adversely affect potential economic benefits • ~~If we do not enter into new collaboration agreements, our revenues and / or cash flows will be reduced relative to prior periods •~~ Our cash flows are likely to differ from our reported revenues and earnings ~~• Our business strategy includes entering into additional collaborative agreements to support development, clinical trials, manufacturing and commercialization of product candidates. We may not be able to successfully negotiate or enter into acceptable collaboration agreements~~ • Failure to comply with governmental regulations could materially harm our business • We have a history of operating losses, expect to continue to have losses and may never achieve or maintain profitability and we may not successfully manage our ~~company~~ **Company** through varying business cycles ~~including macroeconomic uncertainties and the COVID- 19 pandemic • We may develop our own sales force and commercial group to market future products, but we have limited sales and marketing experience and may not be able to do so effectively • Write- offs related to impairment of goodwill, long- lived assets, inventories and other non- cash charges may adversely impact profitability and cause cash flows to differ from reported earnings~~ • We depend upon key personnel who may terminate their employment with us at any time, and we may not be able to attract and retain sufficient qualified personnel on a timely basis, if at all • Cyber- attacks or other failures in telecommunications or information technology systems could result in information theft, data corruption and significant disruption of our business operations • Our business involves environmental risks and risks related to handling regulated substances • **As a non- accelerated filer, we are not required to comply with the auditor attestation requirements of the Sarbanes- Oxley Act and, consequently, some investors may find our common stock less attractive •** If we are unable to protect, maintain or enforce our intellectual property rights or secure rights to third- party intellectual property, **or if our intellectual property rights are inadequate to protect our technology and product candidates, our competitive position could be harmed,** we may lose valuable assets, lose market share or incur costly litigation or our third- party collaborators may choose to terminate their agreements with us ~~, which may depend on our intellectual property~~ • ~~We may~~ **If we are unable to protect the confidentiality of our trade secrets, the value of our technology could** be **materially adversely affected and** ~~sued by third parties claiming that~~ our **business would be harmed • The markets for our pharmaceutical** products ~~or~~ **,** product candidates ~~infringe on their IP rights, particularly because there is substantial uncertainty about the validity~~ and ~~breadth of biopharmaceutical patents •~~ **for our ALZET product line are rapidly changing and** ~~Competitive~~ **competitive , and new** products or technologies **developed by others** could impair our ability to establish, maintain or grow our business **and remain competitive** • Our relationships with physicians, patients and third- party payers are subject to anti- kickback, fraud and abuse, privacy and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings • We could be exposed to significant product liability claims and we are subject to healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties,

contractual damages and reputational harm • Healthcare reform measures could hinder or prevent our product candidates' commercial success • Market acceptance of, and market opportunity for, our products or product candidates is uncertain, and failure to achieve market acceptance or adequate reimbursement from third- party payers will ~~harm~~ **delay our ability to generate** ~~our~~ **or** ~~future~~ **grow** revenues ~~and profitability~~ • Inability to train physicians to use our products may prevent market acceptance of our products • Our stock price has in the past and may in the future not meet the minimum bid price for continued listing on Nasdaq • Our operating history makes evaluating our stock difficult and the price of our stock may be volatile • Investors may experience substantial dilution of their investment • Our ability to use net operating losses and other tax attributes is uncertain and may be limited • We have broad discretion over the use of our cash and investments, which may not always yield a favorable return • Our certificate of incorporation, bylaws and Delaware law could discourage an acquisition of us • Having Delaware as the exclusive forum for substantially all disputes between us and our stockholders could limit our stockholders' ability to obtain a favorable judicial forum for disputes • Because our Company is a " smaller reporting company, " we may take advantage of certain scaled disclosures available to us, resulting in holders of our securities receiving less Company information than they would receive from a public company that is not a smaller reporting company ~~• As a non- accelerated filer, we are not required to comply with the auditor attestation requirements of the Sarbanes- Oxley Act and, consequently, some investors may find our common stock less attractive~~ Risks Related To Our Business Our business depends substantially on the successful development of larsucosterol, which has completed multiple clinical trials, including a Phase ~~1b clinical trial in NASH and a Phase 2a clinical trial in AH, and is continuing to enroll patients for a Phase~~ 2b clinical trial (AHFIRM) in patients with severe AH ~~and anticipate enrolling the last patient~~ **, topline results of which were announced** in ~~the~~ **November 2023. The** AHFIRM trial ~~in~~ **did not achieve** the ~~second quarter~~ **primary endpoint** of ~~2023~~ **a statistically significant difference in 90- day mortality or liver transplant for each dose of larsucosterol versus placebo. Accordingly, future clinical trials may be required to establish clinically and statistically significant proof of efficacy, and sufficient evidence of safety to support regulatory approval. We are communicating** with ~~top- line results to be reported in~~ the ~~second half~~ **FDA about the next steps for the development** of **larsucosterol for** ~~2023. In~~ AH ~~and NASH~~ , **including the size and design of the Phase 3 clinical trial, the specific primary and secondary endpoints for the clinical trial, inclusion and exclusion criteria, duration of follow up, size of the safety databases, statistical analysis plans and** ~~there~~ - **other** ~~are~~ **matters. There is** no **assurance that** ~~currently approved drugs. Ongoing and~~ future clinical trials will ~~need to~~ establish ~~clinically and statistically significant proof of~~ efficacy ~~, and sufficient evidence~~ of ~~safety to support filing for regulatory approval and / or additional clinical trials and ultimately regulatory approval. Larsucosterol~~ **larsucosterol to treat AH or** will ~~require additional development, including completion of the ongoing AHFIRM clinical trial and potentially additional clinical trials as well as potentially further preclinical studies, and other non- clinical parameters, to obtain regulatory clearances before it can be commercialized. We will have to interact with the FDA and other regulatory agencies regarding important aspects of the clinical development program, potentially including the size and design of clinical trials, the specific primary and secondary endpoints for the clinical trials, inclusion and exclusion criteria, stopping rules, duration of follow up, size of the safety databases, statistical analysis plans and other matters. Positive results obtained during early development do~~ not ~~necessarily mean later development will succeed or that regulatory clearances or approvals will be obtained. Changes to any of these aspects of our clinical trial design could~~ result in **unanticipated side** ~~the requirement for additional trials or delay development and approval of larsucosterol. Our drug development efforts may not lead to commercial drugs for several reasons, such as if larsucosterol fails to be shown to be safe and effective~~ **effects** ~~or if we do not have adequate financial or other resources to advance larsucosterol through clinical development and the approval processes. We consider larsucosterol to be our lead and most important asset~~ . If larsucosterol fails to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon development of larsucosterol, which would materially harm our business. **Larsucosterol** ~~Even if the Phase 2b AHFIRM trial successfully demonstrates a reduction in mortality or liver transplantation over placebo plus standard of care, (1) additional clinical trial (s) may be required to support an NDA filing and ultimately to support approval by FDA and / or other regulatory bodies; and (2) accelerated regulatory pathways (such as an FDA priority review designation)~~ may not ~~be available. We do not anticipate that larsucosterol will~~ be eligible to receive regulatory approval from the FDA or ~~comparable foreign authorities~~ **other regulatory agencies** and begin commercialization for a number of years, if ever. This uncertainty may make it difficult to predict the timing or expense required to obtain regulatory approval for larsucosterol. ~~We also may need to revise our clinical development plans after trials have commenced or have been completed, which could add to the time and expense associated with the clinical development of larsucosterol.~~ If we are unable to reach an agreement with the FDA or other regulatory agencies regarding **the development of larsucosterol, including the trial design for a Phase 3 clinical trial in AH for larsucosterol' s** clinical development ~~plans for larsucosterol~~ , we may curtail ~~or~~ **,** limit **or discontinue** our development activities for this product candidate. Even if we ultimately receive regulatory approval for larsucosterol, we or our potential future partners, if any, may be unable to commercialize it successfully for a variety of reasons. These include, for example, the **future** availability of alternative, potentially superior or less expensive treatments, lack of cost- effectiveness, the lack of favorable access and / or commercial pricing, the cost or technical challenges of manufacturing the product on a commercial scale and competition with other treatments. The success of larsucosterol may also be limited by the prevalence and severity of any adverse side effects, including mortality. ~~If we fail~~ **The AHFIRM trial did not achieve the primary endpoint of a statistically significant difference in 90- day mortality or liver transplant for each dose of larsucosterol versus placebo. The failure** to ~~obtain~~ **adequately demonstrate the safety and effectiveness of larsucosterol to the satisfaction of the FDA and other regulatory agencies will result in delays to the** regulatory approval ~~and successfully commercialize~~ **or non- approvability of** larsucosterol **. Future clinical trials may not demonstrate the sufficient levels of safety and efficacy necessary to obtain the requisite regulatory approvals for larsucosterol or may require such significant numbers of patients or additional costs**

to make it impractical to satisfy the regulatory agency' s requirements , ~~the regulatory agency' s requirements,~~ and thus **larsucosterol** ~~our product candidates~~ may not be approved for marketing.During the review process,the FDA or other regulatory agencies may request additional information regarding the efficacy or safety of **larsucosterol** ~~our product candidates~~ and providing such additional information could require significant additional work and expense,and take a significant amount of time,resulting in a material delay of approval or the failure to obtain approval or lead our Company to abandon the development of **larsucosterol** ~~that product candidate~~ . **Additionally** ~~During the review process~~ ,the FDA,or other regulatory agencies,may also request more information regarding the chemistry,manufacturing or controls related to **larsucosterol** ~~our product candidates~~ ,and answering such questions could require significant additional work and expense,and take a significant amount of time,resulting in a material delay of approval or the failure to obtain approval or abandonment of **larsucosterol.Even if larsucosterol receives FDA or other regulatory agency approval,** the **regulatory agency may require that** we **conduct additional clinical** ~~may be unable to raise sufficient capital or generate sufficient revenues to attain or maintain profitability, and our~~ **or** ~~financial condition~~ **non- clinical studies after such approval, place limitations on the use of our products in applicable labels, require marketing under a Risk Evaluation** and ~~stock price~~ **Mitigation Strategy program, include commercially unattractive language in the approved product label, delay approval to market our products or limit the indicated use of our products, which** may ~~decline~~ **harm our business and results of operations** . We will require and may have difficulty or be unsuccessful in raising needed capital in the future to continue to operate as a going concern Our business currently does not generate sufficient revenues to meet our capital requirements and we do not expect that it will do so in the near future. We have expended and will continue to expend substantial funds to conduct the research, development, manufacturing and clinical testing of **larsucosterol** ~~our product candidates, funding and establishing additional clinical- and commercial- scale manufacturing arrangements and facilities, and to provide for the pre- commercial and commercial activities associated with the marketing, sales and distribution of our products and product candidates~~ . Presently, we do not have sufficient cash resources to meet our plans for the next twelve months from the issuance of ~~these~~ -- **the** financial statements **included herein** . Our recurring losses from operations, negative cash flows and need for additional capital raise substantial doubt about our ability to continue as a going concern. As a result, our independent registered public accounting firm included an explanatory paragraph in its report on our financial statements as of, and for the year ended, December 31, ~~2022~~ **2023** . We will require additional financing to fund our operations or we will have to significantly curtail **or discontinue** our operations to conserve our capital resources. Additional funds may not be available on acceptable terms, if at all, and such availability will depend on a number of factors, some of which are outside of our control, including general capital markets conditions and investors' view of our prospects and valuation. Further, investors' perception of our ability to continue as a going concern may make it more difficult for us to obtain financing, or necessitate that we obtain financing on terms that are more favorable to investors, and could result in the loss of confidence by investors, suppliers and employees. Our continued operations are contingent on our ability to ~~enter into new collaborative agreements,~~ raise additional capital **or license or otherwise monetize our assets** ~~and obtain financing and success in future operations~~ . If we do not acquire sufficient additional funding or alternative sources of capital to meet our working capital needs, we will have to substantially curtail **or discontinue** our operations **,** ~~and business plan~~ resulting in delays in **the development of larsucosterol and in** generating ~~future~~ revenue. Our actual capital requirements will depend on many factors, including: • continued progress and cost of our research and development programs; • progress with preclinical studies and clinical trials; • the time and costs involved in obtaining regulatory approvals, if any; • costs involved in establishing manufacturing capabilities for pre- clinical, non- clinical, clinical and commercial quantities of our ~~products and~~ product candidates; • success in entering into collaboration agreements and achieving milestones under such agreements; • ~~the continuation of our collaborative agreements that provide financial funding for certain of our activities; •~~ regulatory actions with respect to our ~~and our collaborators'~~ products and product candidates; • costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing intellectual property rights; • costs of developing sales, marketing and distribution channels and our ability and that of our collaborators to sell our products, products we have a financial interest in and, eventually, product candidates; • competing technological and market developments; • market acceptance of our products, products we have a financial interest in and, eventually, product candidates; • any failure to comply with the covenants in our debt instruments that results in acceleration of repayment obligations ~~; • impacts of the COVID- 19 pandemic~~ ; • costs for recruiting and retaining employees and consultants; and • unexpected legal, accounting and other costs and liabilities related to our business. We may consume available resources more rapidly than currently anticipated, resulting in the need for additional funding **. For example, we do not currently have sufficient funding to complete a Phase 3 trial of larsucosterol, if required by the FDA** . We may seek to raise additional funds through equity or debt financings, convertible debt financings, collaborative arrangements with corporate collaborators or other sources, which, in each case, may be dilutive to existing stockholders and may cause the price of our common stock to decline. In addition, in the event that additional funds are obtained through arrangements with collaborators or other sources, we may have to relinquish rights to some of our technologies, products or product candidates that we would otherwise seek to develop or commercialize ourselves. **We currently rely on third- party contractors to manufacture, package, label and distribute clinical supplies of injectable larsucosterol, and we expect to establish supply agreements for commercial quantities of larsucosterol following approval for marketing by applicable regulatory authorities. We also expect to rely on third- party contractors to manufacture larsucosterol for use in future clinical trials. As of the filing date of this Annual Report on Form 10- K, our third- party manufacturer has not established a final process for the commercial supply of injectable larsucosterol and neither we nor our third- party manufacturer have completed stability testing required to submit and obtain regulatory approval for the use of larsucosterol in the treatment of AH. Reliance on third- party contractors entails risks including, but not limited to: • our inability to identify and negotiate manufacturing and supply agreements with suitable manufacturers ; • delays in the development of manufacturing process technologies and stability testing; • our inability**

to control manufacturing process development and its timing; • manufacturing delays if our third- party contractors give greater priority to the supply of other products over larsucosterol or otherwise do not satisfactorily perform according to the terms of our agreements with such contractors ; • possible terminations or nonrenewals of agreements by our third- party contractors at a time that is costly or inconvenient for us ; • possible breaches by third- party contractors of our agreements with such contractors ; • failures by third- party contractors to comply with applicable regulatory requirements ; • possible mislabeling of clinical supplies, which could result in the supply of incorrect dose amounts or the improper identification of the active drug and / or placebo ; • the possibility that clinical supplies will not be delivered to clinical sites on time, leading to clinical trial interruptions, or that drug supplies will not be distributed to commercial vendors in a timely manner, resulting in lost sales ; or • possible misappropriations of our proprietary information, including our trade secrets and know- how. Additionally, we may incur delays in the regulatory submissions or approval of larsucosterol due to manufacturing process development and stability testing, or from the need to identify or qualify alternative third- party manufacturers. Our current and anticipated future dependence upon third parties for the manufacturing of larsucosterol may adversely affect our future profit margins and our ability to commercialize any of our products that receive marketing approval on a timely and competitive basis. Safety data and indications of activity from completed Phase 1 and 2 clinical trials of larsucosterol, or from geographic or other subset analyses of the AHFIRM trial, may ultimately not be correlated with treatment or improvement in the associated disease, and there is a risk that larsucosterol may not demonstrate therapeutic efficacy in subsequent placebo- controlled trials. For example, the AHFIRM trial did not achieve the primary endpoint of a statistically significant difference in 90- day mortality or liver transplant for each dose of larsucosterol versus placebo. The **failure of larsucosterol to show efficacy in one indication may negatively affect its perceived value in other indications, and the emergence of safety signals in ongoing or future clinical trials would significantly harm our business. From time to time, we may publicly disclose preliminary or " topline " data from our clinical trials, which is based on a preliminary analysis of then- available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report, including the preliminary Phase 2b clinical data for AHFIRM reported in November 2023, may differ from, and may not be indicative of, future results of the same clinical trials, or different conclusions or considerations may qualify such topline results once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available and negative differences between preliminary or interim data and final data could materially adversely affect the prospects of any product candidate that is impacted by such data updates. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and the value of our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically a summary of extensive information, and others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed. Future trials of larsucosterol in patients with AH are subject to potential delays for several reasons, including without limitation: • the** FDA **or other regulatory agencies disagreeing as to the design or implementation of our clinical trials; • failure to agree with the FDA or other regulatory agencies regarding the trial design, including without limitation inclusion and exclusion criteria or primary and secondary endpoints; • failure to reach, or delays in reaching, an agreement on acceptable terms with prospective contract research organizations (" CROs"), and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites; • failure to obtain institutional review board (" IRB") approval at each site; • delays, suspension, or termination of clinical trials by the IRB responsible for overseeing the trial at a particular trial site; • slower than expected rates of recruitment of patients or failure to recruit a sufficient number of patients; • delays in manufacturing or delivery of drug product to clinical trial sites; • patients dropping out of the trial after enrollment or withdrawing consent; • clinical sites deviating from trial protocol, dropping out of a trial, or failing to comply with regulatory requirements; • government, IRB, or other regulatory delays or " clinical holds " requiring suspension or termination of the trials; • COVID- 19, flu or other diseases having an adverse effect on patients'** ~~s Fast Track Designation~~ **willingness to participate in a trial; • protocol amendments; and • the availability of capital to conduct such future trials. There can also be no assurance that biological activity demonstrated in previous animal disease models or earlier clinical trials** of larsucosterol ~~may~~ **will also be seen in future clinical trials, or that any clinically relevant biological activity will be observed, or that enrollment rates in future trials will be favorable or that these additional trials will** not ~~lead~~ **identify safety issues. Failure of future trials** to **achieve desired results in their anticipated timeframe could negatively impact our business and ability to raise additional capital. Moreover, success in future research, preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and we cannot be sure that the results of later clinical trials will replicate the results of prior clinical trials and non- clinical testing. Any future clinical trial process may fail to demonstrate that our potential drug candidates are safe for humans and effective**

for indicated uses. This failure would cause us to abandon a ~~faster~~ **drug candidate and may delay** development **of other potential drug candidates. Any delay in,** or **termination of, future non- clinical testing or clinical trials will delay the filing of any future investigational new drug application (" IND") and new drug application (" NDA") with the FDA or the equivalent applications with pharmaceutical** regulatory ~~review~~ **authorities outside the United States and, ultimately,** ~~or~~ **our** ~~approval~~ **ability to commercialize any potential drugs and generate product revenues. The results of AHFIRM, including the topline data from our AHFIRM Phase 2b trial, may not be indicative of future results.** The FDA grants Fast Track Designation to therapies that are considered capable of addressing unmet medical needs and possess the potential to treat serious or life- threatening disease conditions in order to facilitate its development and expedite the review procedure. Even though larsucosterol has received Fast Track Designation for the treatment of AH, we may not experience a faster development process, review or approval compared to conventional FDA procedures, or receive FDA approval at all, in that indication or any other. A Fast Track Designation does not change the standards for approval. The FDA may also withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. In addition, the statutes and regulations that define the timelines and criteria for approval of drugs and biologics are subject to change by the U. S. Congress and the responsible administrative agencies. For example, the Prescription Drug User Fee Act (" PDUFA ") authorizes the FDA to collect fees and use them for the review of human drug applications and defines the review time targets for such applications. The current legislative authority for PDUFA will expire in September 2027. New legislation will then be required for the FDA to continue collecting prescription drug user fees in future fiscal years and for manufacturers to have clarity regarding the time the FDA will spend in review before granting regulatory approval. If PDUFA reauthorization is not completed in the future, the review and approval times for new drugs like larsucosterol could be significantly longer than currently expected, which could delay potential marketing approval and launch. **Certain previously** ~~Safety data and indications of activity from~~ completed ~~Phase 1 and 2 clinical trials of larsucosterol may not predict safety, activity or therapeutic efficacy in future trials Safety data and indications of activity from completed Phase 1 and 2 clinical trials of larsucosterol may ultimately not be correlated with treatment or improvement in the associated disease, and there is a risk that larsucosterol may not demonstrate therapeutic efficacy in larger placebo- controlled trials such as AHFIRM. The failure of larsucosterol to show efficacy in one indication may negatively affect its perceived value in other indications, and the emergence of safety signals in ongoing or future clinical trials would significantly harm our business. Open- label trials of larsucosterol in NASH~~ **MASH** ~~and AH have inherent limitations The most recently completed NASH~~ and AH trials of larsucosterol were open- label trials with no control groups. Open label trials have inherent risk of bias given that the patients and physicians know that the patients received active study drug, which can lead to placebo effects. Trials without control groups have an inherent risk in that the comparisons used to determine the study drug' s effect and side effect profile are based on comparisons with baseline (pre- treatment) levels (for blood chemistry and biomarker endpoints) and / or with historical controls, which may not have been conducted under similar enough conditions to make accurate comparisons and / or draw accurate conclusions from those comparisons. Additionally, larger placebo- controlled clinical trials are required to evaluate the safety and efficacy of larsucosterol to treat any indication, including AH and ~~NASH~~ **MASH** . There can be no assurance that ongoing or future studies will demonstrate the safety or efficacy of larsucosterol in a statistically significant or clinically meaningful manner ~~. The Phase 2b AHFIRM trial of larsucosterol in patients with AH is subject to potential delays. For example, the uncertainty of COVID- 19 has impacted and may in the future impact our clinical trial sites in the U. S., U. K., E. U. and Australia, which affects the predictability and timing of availability of top- line data from this trial. There can be no assurance that the trial will complete enrollment as anticipated if at all, and delays in enrollment could add to the costs and expenses of this trial and harm our business. There can also be no assurance that biological activity demonstrated in previous animal disease models or earlier clinical trials of larsucosterol will also be seen in ongoing trials or future clinical trials, or that any clinically relevant biological activity will be observed, or that enrollment rates will be favorable or that these additional trials will not identify safety issues. Failure of the AHFIRM trial to achieve desired results in its anticipated timeframe would negatively impact our business and ability to raise additional capital~~ . We may experience delays in completing our preclinical studies and initiating or completing clinical trials, and we may experience numerous unfavorable events during, or as a result of, any future clinical trials that we may conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including: • regulators, institutional review boards (" IRBs"), or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at one or more prospective trial sites; • we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites. We may be forced to accept unfavorable contract provisions in such agreements based on country, territory or local laws or requirements of institutions or IRBs where important clinical investigators practice; • clinical trials of our product candidates **have in the past and** may **in the future** produce negative or inconclusive results, clinical trial subjects receiving placebo or **placebo** ~~standard of care~~ may experience better than expected outcomes, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs; • clinical trial sites or clinical investigators may not comply with the study protocol or applicable laws; • 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 or fail to return for post- treatment follow- up at a higher rate than we anticipate; • our third- party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators; • we may elect to, or regulators or IRBs or ethics committees may require us or our investigators to, 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, regulators or IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other therapies that raise safety or efficacy concerns about our product candidates. We could encounter delays if a clinical trial is **delayed,** suspended or terminated by us, by the IRBs of the institutions at which such trials are being conducted, by the Data Safety Monitoring Board for such trial or by the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination or clinical hold due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities, changes in clinical trial design, safety issues or adverse side effects, failure to demonstrate a benefit from using a product, **or** changes in governmental regulations or administrative actions **. We may also delay, suspend** or **terminate a clinical trial due to a** lack of adequate funding to **commence or** continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials. Our product development costs will also increase if we experience delays in testing or regulatory approvals. We do not know whether any of our future clinical trials will begin as planned, or whether any of our current or future clinical trials will need to be restructured or will be completed on schedule, if at all. Significant preclinical 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 and may harm our business and results of operations. Any delays in our ongoing or future preclinical or clinical development programs may harm our business, financial condition and prospects significantly. **We purchase** ~~While we have entered into contract manufacturing agreements with multiple vendors for~~ larsucosterol ~~,~~ **from a third- party supplier and** we currently have a third- party sole ~~supplier~~ **manufacturer** for GMP supplies of larsucosterol. ~~This~~ **The** third party **supplier is our sole manufacturer of the larsucosterol drug substance and the third party manufacturer** is our sole source for the drug product required for development and commercialization of ~~this~~ **our larsucosterol** drug candidate. The reliance on a sole or limited number of **manufacturers and** suppliers could result in: • an inability to obtain an adequate supply of larsucosterol; • delays associated with finding and contracting with a new supplier **/ manufacturer** (if we can find one capable of replacing the old supplier and negotiate commercially reasonable terms) and then transferring the know- how and technology required to perform the services to the new supplier; and • reduced control over pricing, quality and delivery time. There can be no assurance that we will receive sufficient quantities of larsucosterol to commence and conduct the non- clinical trials, clinical trials and CMC activities we are planning, and delays in supply **or manufacturing** could delay development of larsucosterol ~~. In addition, certain of our third- party manufacturers and suppliers may be experiencing delays as a result of the COVID- 19 pandemic or have otherwise encountered delays in providing their goods and services. As a result, we may not be able to manufacture our product candidates for our clinical trials and conduct other research and development operations and maintain current clinical and pre- clinical timelines~~ . In addition, if additional third parties in our supply chain are adversely impacted by restrictions resulting from ~~the pandemic~~ **macroeconomic events** , including staffing shortages, raw material shortages, production slowdowns and / or disruptions in delivery systems, our supply chain may be disrupted in other ways, further limiting our ability to manufacture our product candidates for our clinical trials and conduct our research and development operations. We have supply agreements in place for certain components of our products and product candidates, but do not have in place long term supply agreements with respect to all of the components of any of our products or product candidates. Therefore, the supply of a particular component could be terminated without **our** ~~DURECT' s~~ consent at any time without penalty to the supplier. In addition, we may not be able to procure required components or drugs from third- party suppliers at a commercially reasonable quantity, quality, cost and timing. In addition, certain of our suppliers may ~~be experiencing delays as a result of the COVID- 19 pandemic or have otherwise encountered~~ -- **encounter** delays in providing their services. Any interruption in the supply of single source components (including active pharmaceutical ingredients, excipients, or components like vials, stoppers, filters and the like), products or product candidates, could cause us to seek alternative sources of supply or attempt to manufacture these items internally if feasible. Furthermore, in some cases, we are relying on our third- party collaborators to procure supply of necessary components. If the supply of any components for our products or product candidates is interrupted, components from alternative suppliers may not be available in sufficient volumes or at acceptable quality levels within required timeframes, if at all, to meet our needs or those of our third- party collaborators. This could delay our ability to obtain commercial product supplies or complete development and obtain approval for commercialization and marketing of our product candidates, causing us to lose sales, incur additional costs, delay new product introductions and could harm our reputation and make access to capital more difficult, expensive or impossible. Supply chain disruptions have affected and are likely to continue to affect the manufacturing and shipment of goods globally. Any delay in production or delivery of the components and drug substances used in our products or product candidates for any reason ~~, including due to an extended closure of our suppliers' plants as a result of efforts to limit the spread of COVID- 19~~ , could adversely impact our business and hinder our growth. Global economic and business activities continue to face widespread macroeconomic uncertainties, including labor shortages and supply chain disruptions, inflation and monetary supply shifts, as well as recession risks, which may continue for an extended period, which may have an adverse impact on the economies and financial markets of many countries, resulting in a severe and prolonged global economic downturn that could continue to affect demand for our ALZET product line and could have an adverse impact on our business operations and financial condition. Further, such macroeconomic uncertainties may also adversely impact our ability to raise additional capital to provide sufficient funding to continue our product development efforts, including clinical trials, which

would make it more difficult for companies such as ours to access capital. ~~For example, the global COVID- 19 pandemic delayed the initiation of our AHFIRM Phase 2b clinical trial to evaluate the safety and efficacy of larsucosterol in severe AH patients and it has delayed, and may in the future delay, the pace of enrollment in this trial and other clinical trials.~~ Additionally, inflation has the potential to adversely affect our liquidity, business, financial condition and results of operations by increasing our overall cost structure. The existence of inflation in the economy has resulted in, and may continue to result in, higher interest rates and capital costs, supply shortages, increased costs of labor, increased manufacturing costs and clinical trial costs, weakening exchange rates and other similar effects. As a result of inflation, we have experienced and may continue to experience cost increases. The extent to which such macroeconomic uncertainties impact our operations will depend on future developments, which are highly uncertain and cannot be predicted with confidence. As a result, there have been and may continue to be longer lead times required for acquiring components and supplies used in manufacturing of larsucosterol, and there have been periods of reduced demand for our ALZET products, which are used in scientific and pre- clinical research. We may continue to experience disruptions that could severely impact our business, preclinical studies and clinical trials including: • delays or difficulties in enrolling patients in our clinical trials; • delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff; • diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials; • interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel **or safety precautions** imposed or recommended by federal, state or local governments, employers and others or interruption of clinical trial subject visits and study procedures, which may impact the integrity of subject data and clinical study endpoints, the ability to collect, ship and analyze biological samples from clinical trial patients due to concerns about potential contamination of samples and / or exposure of clinical staff to patients with **certain diseases** ~~COVID- 19~~ ; • interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines; • disruption or delays in manufacturing of clinical and commercial supplies due to issues experienced by our contract manufacturing organizations and / or shortages and delays in obtaining raw materials and supplies required in the manufacturing processes; • interruption of or delays in receiving supplies of our products and product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages, prioritization of pandemic- related activities over ours and disruptions in delivery systems; • interruptions in preclinical studies due to restricted or limited operations at laboratory facilities; • limitations on employee resources that would otherwise be focused on the conduct of our preclinical studies, clinical trials, and manufacturing activities including because of sickness of employees or their families or the desire of employees to avoid contact with groups of people; and • material delays and complications with respect to our research and development programs. Delays or difficulties in the enrollment of..... our business and results of operations. We have a significant amount of debt. Compliance with repayment obligations and other covenants may be difficult, and failure to fulfill our obligations under the applicable loan agreements may cause our repayment obligations to accelerate In July 2016, we entered into a Loan and Security Agreement (as amended, the " Loan Agreement ") with Oxford Finance LLC (" Oxford Finance"), pursuant to which Oxford Finance provided a $ 20 million secured single- draw term loan to us with an initial maturity date of August 1, 2020. The term loan was fully drawn at close and the proceeds **were** ~~may be~~ used for working capital and general business requirements. ~~The term loan repayment schedule provided initially for interest only payments for the first 18 months, followed by consecutive monthly payments of principal and interest in arrears starting on March 1, 2018 and continuing through the maturity date of August 1, 2020.~~ Following five amendments, we ~~make~~ **made** interest only payments under the amended Loan Agreement until June 1, 2023 **, followed by consecutive monthly payments of principal** and **interest in arrears continuing through September 1, 2025,** the final maturity date of the **term** loan ~~is September 1, 2025~~ . The Loan Agreement provides for a floating interest rate (7. 95 % initially and ~~11~~ **12** . ~~45~~ **75** % as of December 31, ~~2022~~ **2023**) based on an index rate plus a spread and an additional payment equal to 10 % of the principal amount of the term loan, which is due when the term loan becomes due or upon the prepayment of the facility. Any increases in prevailing interest rates could increase our expenses under the Loan Agreement. If we elect to prepay the **term** loan, there is also a prepayment fee between 0. 75 % and 2. 5 % of the principal amount of the term loan depending on the timing of prepayment. Our debt repayment obligations under the Loan Agreement ~~, as amended,~~ may prove a burden to our Company as they become due, particularly following the expiration of the interest- only period. Increased payment requirements that ~~are scheduled to start~~ **started** after June 2023 ~~will~~ increase our cash expenditures and **may eventually** require us to raise additional capital or renegotiate or refinance the Loan Agreement. There can be no assurance that additional capital will be available on acceptable terms, if at all, or that we would be able to successfully renegotiate or refinance the Loan Agreement on acceptable terms, if at all. ~~If our debt repayments increase, we may be required to scale back development programs or other operations, which could have an adverse effect on our business.~~ The Loan Agreement contains customary events of default, including, among other things, our failure to fulfill certain of our obligations under the Loan Agreement and the occurrence of a material adverse change in our business, operations or condition (financial or otherwise), a material impairment of the prospect of repayment of any portion of the **term** loan, the failure to deliver an unqualified audit report and board approved financial projections within time periods set forth in the Loan Agreement, or a material impairment in the perfection or priority of lender' s lien in the collateral or in the value of such collateral. In the event of default by us under the Loan Agreement, the lender would be entitled to exercise its remedies thereunder, including the right to accelerate the debt, upon which we may be required to repay all amounts then outstanding under the Loan Agreement, which could harm our business, operations and financial condition. In addition, the term loan is secured by substantially all of our assets, except that the collateral does not include any equity interests in our Company, any intellectual property (including all licensing, collaboration and similar agreements relating thereto), and certain other excluded assets. The Loan Agreement contains customary representations, warranties and covenants by us, which covenants limit our ability to convey, sell, lease, transfer, assign or otherwise dispose of certain of our assets; engage in any business other than the

businesses currently engaged in by us or reasonably related thereto; liquidate or dissolve; make certain management changes; undergo certain change of control events; create, incur, assume, or be liable with respect to certain indebtedness; grant certain liens; pay dividends and make certain other restricted payments; make certain investments; make payments on any subordinated debt; and enter into transactions with any of our affiliates outside of the ordinary course of business or permit our subsidiaries to do the same. Complying with these covenants may make it more difficult for us to successfully execute our business strategy. We rely on Innocoll for the commercialization of POSIMIR. The current approved labeling for POSIMIR is limited, and Innocoll is responsible for completing post- marketing non- clinical studies and any additional studies required by **the** FDA, and negative results from these studies could adversely affect commercialization of POSIMIR. Innocoll is also responsible for manufacturing POSIMIR. If Innocoll does not successfully grow POSIMIR sales, the royalty payments we receive under our agreement with them will be limited and we may not receive additional milestone payments from them. ~~We~~ **Additionally, we** rely on Indivior for the commercialization of PERSERIS. There can be no assurance that PERSERIS sales will maintain current levels or grow materially. If Indivior does not successfully grow PERSERIS sales, future earn- out payments we receive under our agreement with them will be limited. Both POSIMIR and PERSERIS are subject to boxed warnings that may make them more difficult to commercialize. ~~We~~ **Further, we** rely on Orient Pharma for the commercialization of Methydur. If Orient Pharma does not successfully grow Methydur sales, the royalty payments we receive under our agreement with them will be limited. **The** ~~Further, the~~ sales of each of these products may be negatively impacted by challenging macroeconomic conditions. For certain of our product candidates, we depend to a large extent on third- party collaborators, and we have limited or no control over their development, sales, distribution and disclosure for those product candidates Our performance for certain of our product candidates depends to a large extent on the ability of our third- party collaborators to successfully develop and obtain regulatory approvals. We have entered into agreements with Innocoll, Indivior and Orient Pharma under which we granted such third parties the right to develop, apply for regulatory approval for, market, promote or distribute certain products or product candidates, subject to payments to us in the form of product royalties, earn- out and other payments. We have limited or no control over the expertise or resources that any collaborator may devote to the development, clinical trial strategy, regulatory approval, marketing or sale of these product candidates, or the timing of their activities. Any of our present or future collaborators may not perform their obligations as expected. These collaborators may breach or terminate their agreement with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. Enforcing any of these agreements in the event of a breach by the other party could require the expenditure of significant resources and consume a significant amount of management time and attention. Our collaborators may also conduct their activities in a manner that is different from the manner we would recommend or would have chosen had we been developing such product candidates ourselves. Further, our collaborators may elect not to develop or commercialize product candidates arising out of our collaborative arrangements or not devote sufficient resources to the development, clinical trials, regulatory approval, manufacture, marketing or sale of these product candidates. If any of these events occur, we may not recognize revenue from the commercialization of our product candidates based on such collaborations. In addition, these third parties may have similar or competitive products to the ones which are the subject of their collaborations with us, or relationships with our competitors, which may reduce their interest in developing or selling our products or product candidates. We may not be able to control public disclosures made by some of our third- party collaborators, which could negatively impact our stock price ~~.~~ Our business strategy includes relying on third parties to support development,clinical testing,manufacturing and commercialization of our products and product candidates.Our current business strategy includes reliance on third- party CROs,consultants,service providers and suppliers to provide critical services to support development,clinical testing,and manufacturing of our products and product candidates,including,but not limited to larsucosterol and others.For example,we currently depend on third- party vendors to manage and monitor most of our clinical trials.We rely on third parties to manufacture or perform manufacturing steps relating to our products,product candidates and components.We anticipate that we will continue to rely on these and other third- party contractors to support development,clinical testing,and manufacturing of our products and product candidates.Third parties may not execute their responsibilities and tasks competently in compliance with their contractual obligations to us,applicable laws and regulations or in a timely or cost- effective fashion.Failure of these contractors to provide the required services in a competent or timely manner or on reasonable commercial terms could materially delay the development and approval of our product candidates or commercialization of our products,increase our expenses and materially harm our business,financial condition,results of operations and access to capital **.** . Third- party collaboration agreements typically allow the third party to terminate the agreement (or a specific program within an agreement) at will by providing notice. Termination can result from failure of the collaboration to achieve anticipated milestones, from changes in strategy of the other party or for other reasons. In these cases, the product rights revert to us or certain rights of the partner to use our proprietary technology are terminated. If there have been payments under such agreements that are being recognized over time, termination of such agreements (or programs) can lead to a near- term increase in our reported revenues resulting from the immediate recognition of the balance of such payments. Termination deprives us of potential future economic benefits under such agreements, and may make it more difficult, unattractive or impossible to enter into agreements with other third parties for use of the assets and / or technologies that were subject to the terminated agreement. For example, termination of our agreements with Innocoll or Orient Pharma could have negative effects on our Company. Our revenues ~~have been based to a significant extent on collaborative arrangements with third parties, pursuant to which we receive payments based on our performance of research and development activities set forth in these agreements. For example, approximately 58 % of our total revenues in 2019 were derived from our collaboration agreement with Gilead. In June 2020, Gilead notified us that they were terminating this collaboration, resulting in accelerated recognition of $ 22. 7 million in deferred revenue related to a nonrefundable upfront license fee and a milestone payment totaling $ 35. 0 million that had previously been received. In addition, we have seen periodic fluctuations in revenues associated with our other collaboration agreements, which reflect the current development stage of the product candidates~~

~~subject to those agreements, and our collaborator' s needs for our services. Long- term growth of our collaboration revenues requires us to enter into new collaboration agreements, and there can be no assurance that we will do so. Even if we enter into new collaboration agreements, we may not be able to fulfill our obligations or attain milestones set forth in any specific agreement, which could cause our revenues and / or cash flows to fluctuate or be less than anticipated and may expose us to liability for contractual breach. In addition, these agreements may require us to devote significant time and resources to communicating with and managing our relationships with such collaborators and resolving possible issues of contractual interpretation which may detract from time our management would otherwise devote to managing our operations. Such agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property. Such disputes can delay or prevent the development of potential new product candidates, or can lead to lengthy, expensive litigation or arbitration. In general, our collaboration agreements, may be terminated by the other party at will or upon specified conditions including, for example, if we fail to satisfy specified performance milestones or if we breach the terms of the agreement. Acquisitions of our collaborators or strategic changes or re- organizations or re- prioritizations of our collaborators can lead to turnover of program staff, a review of development programs and strategies by the acquirer, and other events that can disrupt a program, resulting in program delays or discontinuations. If we do not enter into new collaboration agreements, our anticipated revenues and / or cash flows will be reduced relative to periods of increased collaborative research and development revenues, such as occurred in 2020. Our revenues~~ and earnings may differ from our cash flows from revenue- generating activities. Upfront payments received upon execution of collaborative agreements may be recorded as deferred revenue, in which case they would be recognized over the period of performance for the related performance obligations with the third- party collaborator pursuant to the applicable agreement. The period of performance obligations may also be revised on a prospective basis ~~. As of December 31, 2022, we recognized $ 812, 000 of revenue that was previously classified as deferred revenue, which resulted in our reported revenue being greater than cash flows from our ongoing revenue- generating activities~~ . Assumptions related to revenue recognition for performance obligations provided over time are reviewed in each accounting period and changes are recorded in the current period. In certain circumstances, changes in assumptions related to the measure of progress for a performance obligation performed over time could result in negative revenue or the acceleration of revenue for an accounting period. Our business strategy includes relying on third..... of operations and access to capital. Developing, manufacturing, marketing or promoting a drug is subject to very strict regulations and controls. Furthermore, clearance or approval may entail ongoing requirements for post- marketing studies or surveillance. The manufacture and marketing of drugs are subject to continuing FDA and foreign regulatory review and requirements that we update our regulatory filings. Later discovery of previously unknown problems with a product, manufacturer or facility, or our failure to update regulatory files, may result in restrictions, including withdrawal of the product from the market. Any of the following or other similar events, if they were to occur, could delay or preclude us from further developing, marketing or realizing full commercial value of our products or product candidates, which in turn would materially harm our business, financial condition and results of operations: • failure to obtain or maintain requisite governmental approvals; • failure to meet GMP, good laboratory practice and / or other governmental requirements for drug development; • failure to obtain approvals for commercially valuable intended uses of our products and product candidates; or • FDA required product withdrawals, clinical holds or warnings arising from identification of serious adverse side effects in our products and product candidates. Manufacturers of drugs must comply with the applicable FDA GMP regulations, which include production design controls, testing, quality control and quality assurance requirements as well as the corresponding maintenance of records and documentation. Compliance with current GMP regulations is difficult and costly. Manufacturing facilities are subject to ongoing periodic inspection by the FDA and corresponding state and in some cases, foreign agencies, including unannounced inspections, and must be licensed before they can be used for the commercial manufacture of our products and product candidates. We and / or our present or future suppliers and distributors may be unable to comply with the applicable GMP regulations and other FDA and / or foreign regulatory requirements. If we, our third- party collaborators or our respective suppliers do not achieve compliance for our products or product candidates we or they manufacture, the FDA or foreign equivalents may refuse or withdraw marketing clearance or approvals, put our or our partner' s clinical trial on hold, withdraw or reject an investigational NDA or require product recall, which may cause interruptions or delays in the development, manufacture and sale of our products and product candidates. We have ~~a history of operating losses, expect to continue to have losses and may never achieve or maintain profitability and we may not successfully manage our Company through varying business cycles We have~~ incurred significant operating losses since our inception in 1998 and, as of December 31, ~~2022~~ **2023** , had an accumulated deficit of approximately $ ~~561~~ **589** . ~~4~~ **0** million. We expect to continue to incur significant operating losses over the next several years as we continue to incur significant costs for research and development, clinical trials, manufacturing, sales, and general and administrative functions. Our ability to achieve profitability depends upon our ability, alone or with others, to successfully complete the development of our proposed product candidates, obtain the required regulatory clearances, manufacture and market our proposed product candidates and successfully commercialize our approved products. Development of pharmaceutical product candidates is costly and requires significant investment. In addition, we may choose to license from third parties either rights to particular drugs or other appropriate technology and / or intellectual property rights for use in our products and product candidates. The license fees as well as the operating costs of using or developing these technologies or rights would increase the costs of our products and product candidates as well as our operating costs generally. Our ~~current~~ revenues **over the last two years** are from ~~milestones and royalties from Innocoll related to POSIMIR,~~ the ALZET product line ~~, from certain excipient sales~~ , from earn- out payments from Indivior related to sales of PERSERIS, from **certain excipient sales, from** royalty payments from Orient Pharma related to sales of Methydur in Taiwan, ~~and~~ from payments under collaborative research and development agreements with third parties **and from milestones and royalties from Innocoll related to POSIMIR** . We ~~expect our revenues to decrease in the near future, and we~~ do not expect that our revenues will

exceed our operating expenses in the near future. We do not anticipate meaningful revenues to derive from the commercialization and marketing of our products and product candidates in the near future, do not expect to receive additional milestone payments in the near term or meaningful royalties from POSIMIR until the product achieves meaningful sales (if ever) and therefore do not expect to generate sufficient revenues to cover expenses or achieve profitability in the near future. Our success will depend on properly sizing our Company through growth and contraction cycles caused in part by changing business conditions, which places a significant strain on our management and on our administrative, operational and financial resources. For example, in connection with the COVID- 19 pandemic, **from 2020 to 2022,** we required most of our personnel, including all of our administrative employees, to work remotely, restricted on- site staff to only mandatory personnel, implemented social distancing on- site, and closed certain of our offices temporarily. ~~Our increased~~ **While we have switched to a hybrid remote model, our continued** reliance on personnel working remotely makes us more susceptible to reduced productivity, disruptions, delays, and other adverse impacts on our business. In addition, this model could increase our cyber security risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with the FDA, manufacturing sites, research or clinical trial sites. To mitigate **similar** future cycles, we may expand or contract our facilities, our operational, financial and management systems and our personnel. If we are unable to manage growth and contractions effectively, our business would be harmed. Changes in tax law could adversely affect our business and financial condition The rules dealing with U. S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U. S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. ~~In recent years, many~~ **Many** such changes have been made **in the past** and changes are likely to continue to occur in the future. For example, on March 11, 2021, President Biden signed into law the " American Rescue Plan Act ", which included extenders to the refundable employee retention credit under the Coronavirus Aid, Relief, and Economic Security (" CARES") Act and limitations to executive compensation effective for tax years beginning after 2026. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We may develop our own sales force and commercial group to market future products but we have limited sales and marketing experience and may not be able to do so effectively We have a small sales and marketing group focused on our ALZET product line. We may choose to develop our own sales force and commercial group to market larsucosterol, if approved, or other products that we may develop in the future. Developing a sales force and commercial group would require substantial expenditures and the hiring of qualified personnel. We have limited sales and marketing experience, and may not be able to effectively recruit, train or retain sales and marketing personnel. If we are not able to put in place an appropriate sales force and commercial group for our products in development and provide that commercial team with sufficient financial and other resources, we may not be able to effectively launch or commercialize these or any other products. We may not be able to effectively sell our products and product candidates, if approved, and our failure to do so could limit or materially harm our business. We and our third- party collaborators may not sell our product candidates effectively We and our third- party collaborators (including Innocoll, Indivior and Orient Pharma) compete with many other companies that currently have extensive and well- funded marketing and sales operations. Our marketing and sales efforts and those of our third- party collaborators may be unable to compete successfully against these other companies. We and our third- party collaborators, where applicable, may be unable to establish a sufficient sales and marketing organization on a timely basis, if at all. We and our third- party collaborators, where applicable, may be unable to engage qualified distributors. Even if engaged, these collaborators and distributors may: • fail to adequately market our products or product candidates; • fail to satisfy financial or contractual obligations to us; • cease operations, terminate our collaboration or re- allocate resources away from our products or product candidates with little or no notice to us; • offer, design, manufacture or promote competing product lines; • fail to maintain adequate inventory and thereby restrict use of our products or product candidates; or • build up inventory in excess of demand thereby limiting future purchases of our products or product candidates resulting in significant quarter- to- quarter variability in our sales. The failure ~~of~~ **by** us or our third- party collaborators to effectively develop, gain regulatory approval for, sell, manufacture and market our products and product candidates will hurt our business, prospects, financial results and may impact our access to capital . We may incur significant non-..... our ability to meet our financing objectives . Our success will depend to a significant degree upon the continued services of key management, technical and scientific personnel. In addition, our success will depend on our ability to attract and retain other highly skilled personnel, particularly as we develop and expand our Epigenetic Regulator Program. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. The market for qualified personnel in the San Francisco Bay Area is very competitive and we may be unable to recruit such personnel on a timely basis, if at all. Our management and other employees may voluntarily terminate their employment with us at any time ~~. Further, in 2021 and 2022, the labor market in the U. S. experienced a significant increase in workers leaving their positions (often referred to as the " Great Resignation "), which made the market to replace these individuals competitive and resulted in significant wage inflation in response to labor shortages. During the Great Resignation we faced and may continue to face increased challenges of employee attraction and retention~~ . The loss of the services of key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to product development or approval, loss of sales and diversion of management resources as well as difficulties or inability to raise sufficient capital to fund our Company' s operations. 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, and may cause a disruption in our operations, harm our reputation, cause us to pay to retrieve our data if it becomes infected or otherwise subject to ransomware, and increase our stock trading risk. There

can be no assurance that we will be successful in preventing cyber- attacks or successfully mitigating their effects. Similarly, there can be no assurance that our third- party collaborators, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber- attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber- attacks or other data security breaches and may incur significant additional expense to implement further data protection measures . Our corporate headquarters, certain manufacturing..... efforts, could be harmed or destroyed . In connection with our research and development activities and our manufacture of materials, products and product candidates, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with the applicable laws, regulations and policies in all material respects and have not been required to correct any material noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the use, generation and disposal of hazardous materials, including but not limited to certain hazardous chemicals, solvents, agents and biohazardous materials. Although we believe that our safety procedures for storing, handling and disposing of such materials comply with the standards prescribed by state and federal regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials. We currently contract with third parties to dispose of these substances generated by us, and we rely on these third parties to properly dispose of these substances in compliance with applicable laws and regulations. If these third parties do not properly dispose of these substances in compliance with applicable laws and regulations, we may be subject to legal action by governmental agencies or private parties for improper disposal of these substances. The costs of defending such actions and the potential liability resulting from such actions are often very large. In the event we are subject to such legal action or we otherwise fail to comply with applicable laws and regulations governing the use, generation and disposal of hazardous materials and chemicals, we could be held liable for any damages that result, and any such liability could exceed our resources. We are a non- accelerated filer as defined by Rule 12b- 2 of the Exchange Act, and as such, are not required to provide an auditor attestation of management' s assessment of internal control over financial reporting, which is generally required for SEC reporting companies under Section 404 (b) of the Sarbanes- Oxley Act. Therefore, our internal controls over financial reporting will not receive the level of review provided by the process relating to the auditor attestation included in annual reports of issuers that are subject to the auditor attestation requirements. Because we are not required to have our auditors provide an attestation of our management' s assessment of internal control over financial reporting, a material weakness in internal control may remain undetected for a longer period. In addition, investors may find our common stock less attractive because we are not required to comply with the auditor attestation requirements. 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 the trading price for our common stock as well as our ability to raise capital may be negatively affected. .Our corporate headquarters,certain manufacturing facilities and personnel are located in a seismically active area near wildfire zones Our corporate headquarters,certain manufacturing facilities and personnel are located in a geographical area that is known to be seismically active and prone to earthquakes,as well as wildfires and related power outages or power shortages.Should such a natural disaster or power outage or power shortage occur,our ability to conduct our business could be severely restricted,and our business and assets,including the results of our research,development and manufacturing efforts,could be harmed or destroyed If we seek approval to commercialize our current or future drug candidates outside of the United States, a variety of risks associated with international operations could harm our business If we seek approval of our current or future drug candidates outside of the United States, we expect that we will be subject to additional risks including: • different regulatory requirements for approval of therapies in foreign countries; • the potential for reduced protection for intellectual property rights; • the potential requirement of additional clinical studies in international jurisdictions; • unexpected changes in tariffs, trade barriers and regulatory requirements; • economic weakness, including inflation, or political instability in particular foreign economies and markets; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; • foreign reimbursement, pricing and insurance regimes; • workforce uncertainty in countries where labor unrest is more common than in the United States; • production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and • business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters and public health pandemics ~~, such as COVID- 19~~ . We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by many of the individual countries in and outside of Europe with which we will need to comply. Many biopharmaceutical companies have found the process of marketing their own products in foreign countries to be very challenging. Risks Related to Our Intellectual Property Our ability to commercially exploit our products will depend significantly on our ability to obtain and maintain patents, maintain trade secret protection and operate without infringing the proprietary rights of others. **The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. There can be no assurance that the pending patent applications will be granted, and if granted, they may fail to result in issued patents with claims that cover our product candidates or technologies.** As of March ~~3~~ **26** , ~~2023~~ **2024** , we owned or exclusively in- licensed over ~~25~~ **15** unexpired issued U. S. patents and over ~~170~~ **165** unexpired issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have over ~~30~~ **20** pending U. S. patent applications and over ~~190~~ **135** foreign applications pending in Europe, Australia, Japan, Canada and other countries. There can be no assurance that the pending patent applications will be granted. Further, there can be no assurance that VCU will not attempt to terminate their license to us, which termination could result in the loss of our rights to certain of these patent families. The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In

addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued. **Even if patents have been issued, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Changes in either the patent laws or interpretation of the patent laws in the United States or elsewhere could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Further, there can be no assurance that VCU will not attempt to terminate their license to us, which termination could result in the loss of our rights to certain of these patent families.** Consequently, our patent applications or those that are licensed to us may not issue into patents, and any issued patents may not provide protection against competitive technologies or may be held invalid if challenged. Our competitors may also independently develop products similar to ours or design around or otherwise circumvent patents issued to us or licensed by us. **Moreover, patents have a limited lifespan. In the United States and in many other countries, the natural expiration of a patent is generally 20 years after it is filed, and once any patents covering a product expire, generic competitors may enter the market. We may not be able to protect our intellectual property rights throughout the world. Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States may be less extensive than those in the United States.** In addition, the laws of some foreign countries may not protect our proprietary rights to the same extent as U. S. law, if at all **. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as in the United States** . We also rely upon trade secrets, technical know- how and continuing technological innovation to develop and maintain our competitive position. We require our employees, consultants, advisors and collaborators to execute confidentiality and assignment- of- inventions agreements with us. These agreements typically provide that all materials and confidential information developed or made known to the individual during the course of the individual' s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances, and that all inventions arising out of the individual' s relationship with us will be our exclusive property. These agreements may be breached, and in some instances, we may not have an appropriate remedy available for breach of the agreements. Furthermore, our competitors may independently develop substantially equivalent proprietary information and techniques, reverse engineer our information and techniques, or otherwise gain access to our proprietary technology. We **also seek to preserve the integrity and confidentiality of our confidential proprietary information by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. If any of our confidential proprietary information were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position. We** may be unable to meaningfully protect our rights in trade secrets, technical know- how and other non- patented technology. We may **be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties We employ individuals who were previously employed at other biotechnology or biopharmaceutical companies. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that we or our employees, consultants, or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees. Even if we are successful in defending against these types of claims, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and, if securities analysts or investors perceive these results to be negative, that perception could have a substantial adverse effect on the price of our common stock. This type of litigation or proceeding could substantially increase our operating losses and reduce our resources available for development activities. Some of our competitors may be able to sustain the costs of this type of litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of intellectual property litigation or other intellectual property related proceedings could adversely affect our ability to compete in the marketplace. We may be subject to claims challenging the inventorship of our patents and other intellectual property We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in- licensed patents, trade secrets, or other intellectual property as an inventor or co- inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in- licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects. Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies and our patent protection could be reduced or eliminated for non- compliance with these requirements The USPTO and various foreign**

governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in premature abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non- compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non- payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our product candidates, which would have a material adverse effect on our business. We may be involved in lawsuits and other legal proceedings to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful. Any such adverse result or determination could have a material adverse effect on our business. Competitors may infringe our issued patents or any patents issued as a result of our pending or future patent applications. We may have to resort to litigation or arbitration to protect our intellectual property rights, or to determine their scope, validity or enforceability. In addition, interference, derivation, post- grant oppositions, and similar proceedings may be necessary to determine rights to inventions in our patents and patent applications. Enforcing or defending our proprietary rights is expensive, could cause diversion of our resources and may be unsuccessful **. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable or may refuse to stop the other party in such infringement proceeding from using the technology at issue on the grounds that our patents do not cover the technology in question** . Any failure to enforce or protect our rights could cause us to lose the ability to exclude others from using our technology to develop or sell competing products. In addition, in some circumstances our collaborators have the first right to enforce our patents against third party infringers, and such collaborators may not enforce such claims adequately or successfully or in the manner that we would do ourselves **We may be sued** by third parties claiming that our products or product candidates infringe on their intellectual property rights,particularly because there is substantial uncertainty about the validity and breadth of biopharmaceutical patents ~~Numerous third- party U.S.and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates,and there may be third- party patents or patent applications with claims to compositions,formulations,methods of manufacture or methods for treatment related to the use or manufacture of our product candidates and technologies.~~ We or our collaborators may be exposed to future litigation by third parties based on claims that our products,product candidates or activities infringe the intellectual property rights of others.We may also be subject to claims asserting that we,our collaborators,our employees,consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.These risks are exacerbated by the fact that the validity and breadth of claims covered in medical technology,pharmaceutical and biotechnology patents and the breadth and scope of trade secret protection involve complex legal and factual questions for which important legal principles are unresolved.Any litigation or claims against us or our collaborators,whether or not valid,could result in substantial costs,could place a significant strain on our financial resources and could harm our reputation and business prospects.We also may not have sufficient funds to litigate,particularly against parties with substantially greater resources.In addition,pursuant to our collaborative agreements,we have provided our collaborators with the right,under specified circumstances,to defend against any claims of infringement of the third- party intellectual property rights,and such collaborators may not defend against such claims adequately or successfully or in the manner that we would do ourselves.Intellectual property litigation or claims could force us or our collaborators to do one or more of the following,any of which could harm our business or financial results:• cease selling,incorporating or using any of our products or product candidates **that incorporate the challenged intellectual property;• obtain a license from the holder of the infringed intellectual property right,which license may be costly or may not be available on reasonable terms,if at all;or • redesign our products or product candidates,which would be costly and time- consuming and may not be successful.** . Our collaboration agreements may depend on our intellectual property We are party to collaborative agreements with Innocoll and Orient Pharma, among others. Our third- party collaborators have entered into these agreements based on the exclusivity that our intellectual property rights confer on the products being developed. The loss or diminution of our intellectual property rights could result in a decision by our third- party collaborators to terminate their agreements with us. In addition, these agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property and data under collaborations. Such disputes can lead to lengthy, expensive litigation or arbitration requiring us to devote management time and resources to such disputes which we would otherwise spend on our business. We may be sued by third parties..... consuming and may not be successful. Risks Related To Our Industry ~~The markets for our pharmaceutical products, product candidates and for our ALZET product line are rapidly changing and competitive, and new products or technologies developed by others could impair our ability to establish, maintain or grow our business and remain competitive~~ The pharmaceutical industry is subject to rapid and substantial technological change. Developments by others may render our products, product candidates under development or technologies noncompetitive or obsolete, or we may be unable to keep pace with technological developments or other market factors. Technological competition in the industry from pharmaceutical and biotechnology companies, universities, governmental entities and others diversifying into the field is intense and is expected to increase. We may face competition from other companies in numerous industries including pharmaceuticals, biotechnology, medical devices and drug delivery. Competition for larsucosterol, if approved, will depend on the specific indication (s) for which larsucosterol is approved. **Afimmune Ltd., Alfasigma S. p. A.,** Akaza Bioscience Ltd ~~., Aldeyra Therapeuties, Inc~~ ., Boehringer Ingelheim International GmbH, Immuron Ltd., ~~Intercept Pharmaceuticals, Inc.,~~ Mallinckrodt plc **, MedRegen LLC**

, Novartis Pharma AG, PharmaKing Co. Ltd, Surrozen, Inc., and others have development plans for products to treat AH. Competition for our ALZET product line primarily consists of customers choosing to utilize delivery methods for their research projects other than an osmotic pump. We also face competition for our ALZET product line from other companies including low cost foreign competitors. We are engaged in the development of novel therapeutic technologies. Our resources are limited and we may experience technical challenges inherent in such novel technologies. Competitors have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products. Some of these products may have an entirely different approach or means of accomplishing similar therapeutic effects than our products and product candidates. Our competitors may develop products that are safer, more effective or less costly than our products and product candidates and, therefore, present a serious competitive threat to our product candidates and product offerings. The widespread acceptance of therapies that are alternatives to ours may limit market acceptance of our products and product candidates if commercialized. For example, post- operative pain is currently being treated by oral medication, transdermal drug delivery systems, such as drug patches, long- acting and short- acting injectable products and implantable drug delivery devices which are competitive with our products and product candidates. Many of these treatments are widely accepted in the medical community and have a long history of use. The established use of these competitive products may limit the potential for our products and product candidates to receive widespread acceptance if and when commercialized. Healthcare providers, physicians and third- party payers will play a primary role in the recommendation and prescription of POSIMIR and any additional product candidates for which we obtain marketing approval. Our future arrangements with third- party payers and customers may expose us and our partners to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we and our partners may market, sell and distribute our products. As a pharmaceutical company, even though we do not and may not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third- party payers, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. These regulations include: • the Federal Healthcare 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 a federal healthcare program such as Medicare and Medicaid, and which will constrain our marketing practices and the marketing practices of our licensees, educational programs, pricing policies, and relationships with healthcare providers or other entities; • the federal physician self- referral prohibition, commonly known as the Stark Law, which prohibits physicians from referring Medicare or Medicaid patients to providers of " designated health services " with whom the physician or a member of the physician' s immediate family has an ownership interest or compensation arrangement, unless a statutory or regulatory exception applies; • federal false claims laws that prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other government reimbursement programs that are false or fraudulent, and which may expose entities that provide coding and billing advice to customers to potential criminal and civil penalties, including through civil whistleblower or qui tam actions, and including as a result of claims presented in violation of the Federal Healthcare Anti- Kickback Statute, the Stark Law or other healthcare- related laws, including laws enforced by the FDA; • the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services, and which as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information; • federal physician sunshine requirements under the Affordable Care Act, which requires manufacturers of drugs, devices, biologics and medical supplies to report annually to HHS information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; • the Federal Food, Drug, and Cosmetic Act, which, among other things, strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off- label use and regulates the distribution of drug samples; • state and foreign law equivalents of each of the above federal laws, such as 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 payers, including private insurers, state laws requiring pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and which may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, many of which differ from each other in significant ways and often are not preempted by federal laws such as HIPAA, thus complicating compliance efforts; and • HIPPA and other state and foreign laws governing the privacy and security of health information or other personal information, such as the European Union General Data Protection Regulation ~~, or~~ **("** GDPR ~~,~~ **")** (EU 2016 / 679), which require limitations regarding access and use of certain personal and health information. Efforts to ensure that our business arrangements with third parties comply with applicable healthcare and privacy laws and regulations do and will in the future 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 or privacy laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other

healthcare providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs . In the United States and some..... Government Regulation — Healthcare Reform " above . We could be exposed to significant product liability claims which could be time consuming and costly to defend, divert management attention and adversely impact our ability to obtain and maintain insurance coverage The testing, clinical development, manufacture, marketing and sale of our products and product candidates involve an inherent risk that product liability claims will be asserted against us. Our present product liability insurance may be inadequate and may not fully cover the costs of any claim (s) or any ultimate damages we might be required to pay. Product liability claims or other claims related to our products and product candidates, regardless of their outcome, could require us to spend significant time and money in litigation or to pay significant damages. Any successful product liability claim may prevent us from obtaining adequate product liability insurance in the future on commercially desirable or reasonable terms. In addition, product liability coverage may cease to be available in sufficient amounts or at an acceptable cost. An inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of our products or product candidates if and when approved. A product liability claim could also significantly harm our reputation and delay or prevent market acceptance of our products and product candidates. . In the United States and some foreign jurisdictions,there have been,and we expect there will continue to be,a number of legislative and regulatory changes to the healthcare system,including cost- containment measures that may reduce or limit coverage and reimbursement for newly approved drugs,that could prevent or delay marketing approval of our product candidates,restrict or regulate post- approval activities,affect our ability to profitably sell any product or product candidates for which we obtain marketing approval and otherwise affect our future revenue and profitability and the future revenue and profitability of our collaborators or potential collaborators.In particular,there have been and continue to be a number of initiatives at the U.S.federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare.For examples of healthcare reform measures,see " Part I,Item 1.Business — Government Regulation — Healthcare Reform " above .—Market acceptance of, and market opportunity for, our products or product candidates is uncertain, and failure to achieve market acceptance will delay our ability to generate or grow revenues Our future financial performance will depend upon the successful introduction and customer acceptance of our products or products we have licensed to others, including larsucosterol, if approved, and Innocoll' s POSIMIR, Indivior' s PERSERIS and Orient Pharma' s Methydur. Even if approved for marketing, these products and product candidates may not achieve market acceptance or the market opportunities for our current and potential future product candidates may be smaller than we predicted, which could adversely affect our future product revenues and could cause our business to suffer. The degree of market acceptance will depend upon a number of factors, including: • the degree of unmet need in the market for the approved indication (s); • the receipt of regulatory clearance of marketing claims for the uses that we are developing; • the approved product labeling; • pricing, reimbursement and formulary access; • the degree of resources applied to promotion and other commercial activities; • the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapies; and • pricing, access and reimbursement policies of government and third- party payors such as insurance companies, health maintenance organizations, hospital formularies and other health plan administrators. Physicians, patients, payers or the medical community in general may be unwilling to accept, utilize or recommend any of the products we have developed. If these products do not achieve widespread market acceptance, we will not achieve meaningful revenues . If users of our products are..... ability to operate profitably and access capital . If we or our third- party collaborators are unable to train physicians to use our products and product candidates to treat patients' diseases or medical conditions, we may not achieve market acceptance of our products Broad use of certain of our products or out- licensed products, such as POSIMIR, will require extensive training of numerous physicians on their proper and safe use. The time required to train physicians could delay adoption of our products and adversely affect market acceptance of our products. We or third parties selling our products may be unable to rapidly train physicians in numbers sufficient to generate adequate demand for our products. Any delay in training would materially delay the demand for our products and harm our business and financial results. In addition, we or our partners may expend significant funds towards such training before any orders are placed for our products, which would increase our expenses and harm our financial results. . If users of our products are unable to obtain adequate reimbursement from third- party payers,obtain access to our product (s),or if new restrictive legislation is adopted,market acceptance of our products may be limited and we may not achieve meaningful revenues or profitability The continuing efforts of government and insurance companies,health maintenance organizations and other payers of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability,and the future revenues and profitability of our potential customers,suppliers and third- party collaborators and the availability of capital.For example,in certain foreign markets,pricing,access and / or profitability of prescription pharmaceuticals is subject to government control.In the United States,recent federal and state government initiatives have been directed at lowering the total cost of health care,and the U.S.Congress and state legislatures will likely continue to focus on health care reform,the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid systems.While we cannot predict whether any such legislative or regulatory proposals will be adopted,the announcement or adoption of such proposals could materially harm our business,financial condition and results of operations.The successful commercialization of our current and future products will depend in part on the extent to which appropriate reimbursement levels for the cost of our products and related treatment are obtained from governmental authorities,private health insurers and other organizations,such as health maintenance organizations (" HMOs ").Third- party payers often limit access,payments and / or reimbursement for medical products and services.Also,the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs,which could control or significantly influence the purchase of health care services and products,as well as legislative proposals to reform health care or reduce government insurance programs,may limit access,reimbursement or payment for our products.The cost

containment measures that health care payers and providers are instituting and the effect of any health care reform could materially harm our ability to operate profitably and access capital .Risks related to actions on trade by the U. S. and foreign governments could adversely affect our Company' s results of operations and financial condition The U. S. government under the previous administration indicated its intent to adopt a new approach to trade policy and in some cases to renegotiate, or potentially terminate, certain existing bilateral or multilateral trade agreements. It also initiated the imposition of tariffs on certain foreign products. Changes in U. S. trade policy have resulted in, and could continue to result in, one or more U. S. trading partners adopting responsive trade policy **or tariffs** making it more difficult or costly for us to export our products to those countries. **The imposition of additional tariffs by the United States could result in the adoption of additional tariffs by other countries.** These measures could also result in increased costs for goods imported into the United States . This in turn could require us to increase prices to our customers which may reduce demand, or, if we are unable to increase prices, result in lowering our margin on products sold. There is also a concern that the imposition of additional tariffs by the United States could result in the adoption of additional tariffs by other countries . A potential resulting trade war could have a significant adverse effect on world trade and the world economy **. This in turn could require us to increase prices to our customers which may reduce demand, or, if we are unable to increase prices, result in lowering our margin on products sold** . We cannot predict future trade policy or the terms of any renegotiated trade agreements and their impact on our business. The adoption and expansion of trade restrictions, the occurrence of a trade war, or other governmental action related to tariffs or trade agreements or policies has the potential to adversely impact demand for our products, our costs, our customers, our suppliers, and the U. S. economy, which in turn could adversely impact our business, financial condition, access to capital and results of operations. Risks Related To Our Common Stock Our stock price has in the past and may in the future not meet the minimum bid price for continued listing on Nasdaq. Our ability to continue operations or to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if we are delisted from Nasdaq In several instances in the past, including as recently as February 9 **December 21** , 2022 **2023** , we received written notifications from Nasdaq informing us that because the closing bid price of our common stock was below $ 1. 00 for 30 consecutive trading days (the " Minimum Closing Bid Price Requirement "), our shares no longer complied with the Minimum Closing Bid Price Requirement for continued listing on Nasdaq under Nasdaq Marketplace Rules. Each time, we were given a period of 180 days from the date of the notification and in one case an extra 180- day period to regain compliance with Nasdaq' s listing requirements by having the closing bid price of our common stock listed on Nasdaq be at least $ 1. 00 for at least 10 consecutive trading days. **If** While we have regained compliance within the applicable time periods in the past, if our shares again no longer comply with the Minimum Closing Bid Price Requirement for continued listing on the Nasdaq Capital Market under Nasdaq Marketplace Rule 5550 (a) (2) and we do not regain compliance **with the Minimum Closing Bid Price Requirement for continued listing on the Nasdaq Capital Market under Nasdaq Marketplace Rule 5550 (a) (2)** within the applicable 180- day time period, Nasdaq will notify us that our securities will be subject to delisting. One strategy to regain compliance in such circumstances would be to implement a reverse stock split. For example, we implemented such a strategy to regain compliance with the Minimum Closing Bid Price Requirement when we completed a 1- for- 10 reverse stock split **on in** December 5, 2022 (the " Stock Split ") . We could also appeal Nasdaq' s determination to delist our securities to a Hearings Panel. During any appeal process, shares of our common stock would continue to trade on the Nasdaq Capital Market. There can be no assurance that we will maintain **regain** compliance with the requirements for listing our common stock on the Nasdaq Capital Market. Delisting from Nasdaq would constitute an event of default under our loan facility with Oxford, entitling Oxford to accelerate our obligations under such facility, among other actions. Under such circumstances, we could be required to renegotiate the repayment terms of our loan facility, on terms which would not be as favorable to our Company as our current terms, or we could be required to take other actions, such as discontinuing some or all of our operations, selling assets, or other action **actions** . Delisting could also adversely affect our ability to raise additional capital through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities. Additionally, there can be no assurance that the **a reverse** Stock **stock** Split **split** will **would** result in a per- share market price that will maintain compliance with the Minimum Closing Bid Price Requirement, that will attract institutional investors or investment funds or that such share price will satisfy investing guidelines of institutional investors or investment funds. As a result, the trading liquidity of our common stock **could decline** may not improve . Further, if the market price of our common stock declines, the percentage decline may be greater than would have occurred in the absence of a reverse stock split. Our quarterly and annual results of operations have historically fluctuated and we expect will continue to fluctuate for the foreseeable future. We believe that period- to- period comparisons of our operating results should not be relied upon as predictive of future performance. Our prospects must be considered in light of the risks, expenses and difficulties encountered by companies with a limited number of approved pharmaceutical products, particularly companies in new and rapidly evolving markets such as pharmaceuticals and biotechnology. To address these risks, we must, among other things, obtain regulatory approval for and commercialize our product candidates, which may not occur. We may not be successful in addressing these risks and difficulties. We expect to require additional funds to complete the development of larsucosterol or our other product candidates, and to fund operating losses to be incurred in the next several years. long as (i) our voting and non- voting common stock held by non- affiliates is less than $ 250 million measured on the last business day of our second fiscal quarter,or (ii) our annual revenue is less than $ 100 million during the most recently completed fiscal year and our voting and non- voting common stock held by non- affiliates is less than $ 700 million measured on the last business day of our second fiscal quarter.To the extent we take advantage of any reduced disclosure obligations,it may make it harder for investors to analyze our Company' s results of operations and financial prospectus in comparison with other public companies. The price of our common stock may be volatile The stock markets in general,and the markets for pharmaceutical

stocks in particular,have experienced extreme volatility that has often been unrelated to the operating performance of particular companies.These broad market fluctuations may adversely affect the trading price of our common stock.Price declines in our common stock **have in the past and** could **in the future** result from general market and economic conditions and a variety of other factors,including:• adverse results (including adverse events or failure to demonstrate safety ~~or ,~~ efficacy **or statistical significance**) or delays in our clinical and non- clinical trials of larsucosterol or other product candidates;• announcements of FDA non- approval of our product candidates,approvals with narrow indications,commercially limiting labels,clinical holds or delays in the FDA or other foreign regulatory agency review process;• adverse actions taken by regulatory agencies or law enforcement agencies with respect to our products and product candidates,clinical trials,manufacturing processes,accounting practices or sales and marketing activities,or those of our third- party collaborators;• announcements of technological innovations,patents,product approvals,sales performance or new products by our competitors;• failure of third- party collaborators to continue development or successful commercialization of the respective products and product candidates they are developing or commercializing;• failure by our commercial licensee (Innocoll) to successfully manufacture and store adequate supplies,and / or to achieve sales expectations and successfully commercialize POSIMIR;• regulatory,judicial and patent developments in the United States and foreign countries;• any lawsuit or arbitration involving us or our products and product candidates including intellectual property infringement or product liability suits;• announcements concerning our competitors,or the biotechnology or pharmaceutical industries in general;• developments concerning our strategic alliances or termination of such alliances or acquisitions or dispositions;• actual or anticipated variations in our operating results;• changes in recommendations by securities analysts,misstatements or mischaracterizations in analyst reports or dropping or lack of analyst coverage;• negative press coverage or online or social media misinformation about the Company or its partners or their respective products or personnel;• deviations in our operating results from the estimates of analysts;• sales of our common stock by our executive officers or directors or sales of substantial amounts of common stock by us or others;• potential failure to meet continuing listing standards from The Nasdaq Capital Market;• loss or disruption of facilities due to natural disasters;• acceleration of our debt obligations due to a determination by our lender that a material adverse change has occurred;• changes in accounting principles;or • loss of any of our key scientific or management personnel.The market price of our common stock may fluctuate significantly in response to factors which are beyond our control.The stock market in general has periodically experienced extreme price and volume fluctuations.For example,the COVID- 19 pandemic,pronouncements by the Federal Reserve,inflation,outbreaks of war such as between Russia and Ukraine **or Israel and Hamas** ,oil price volatility and other factors have caused broad stock market and industry fluctuations.In addition,the market prices of securities of technology and pharmaceutical companies have also been extremely volatile,and have experienced fluctuations that often have been unrelated or **disproportionate to the operating performance of these companies.These broad market fluctuations could result in extreme fluctuations in the price of our common stock,which could cause a decline in the value of our common stock.In the past,following periods of volatility in the market price of a particular company' s securities,litigation has often been brought against that company.If litigation of this type is brought against us,it could be extremely expensive,particularly if we were to lose the lawsuit and have to pay damages,and divert management' s attention and our Company' s resources.** In order to raise capital and for other purposes, we may in the future offer and issue additional shares of our common stock or other securities convertible into or exchangeable for our common stock, and the price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share at which investors in our common stock bought their shares. In July 2021, we filed the 2021 Registration Statement to sell up to $ 250 million of securities from time to time in one or more public offerings, including up to $ 75. 0 million of shares of common stock through the 2021 Sales Agreement. Any sales in the public market of our common stock, under the 2021 Sales Agreement, in offerings under our shelf registration statement or otherwise, could adversely affect prevailing market prices for our common stock. **In** ~~Through several financings between 2019 and 2022~~ **2023** , ~~and through~~ **we raised net proceeds (net of commissions) of approximately $ 1. 6 million from the sale of** our ~~2015 Sales Agreement, 2018 Sales Agreement and~~ **common stock in the open market under the** 2021 Sales Agreement ~~with Cantor Fitzgerald during this period~~ **. In February and March 2024** , we ~~have~~ raised ~~an aggregate~~ **net proceeds (net** of **commissions) of approximately** $ ~~79~~ **648, 000 from the sale of our common stock in the open market under the 2021 Sales Agreement** . ~~5~~ **As of March 26, 2024, we had up to $ 222. 7** million ~~. Further~~ **of our securities available for sale under the 2021 Registration Statement** , ~~on~~ **of which $ 72. 7 million of our common stock are available pursuant to the 2021 Sales Agreement. On** February 3, 2023, we consummated a registered direct ~~offering~~ financing pursuant to which we sold an aggregate of 1, 700, 000 shares of our common stock, pre- funded warrants to purchase up to 300, 000 shares of our common stock and common warrants to purchase up to 2, 000, 000 shares of our common stock. Each share of common stock and accompanying common warrant and each pre- funded warrant and accompanying common warrant were sold together at a combined offering price of $ 5. 00 per share and accompanying warrant or, in the case of pre- funded warrants, $ 4. 99999 per pre- funded warrant and accompanying common warrant. ~~You~~ **Additionally, on July 19, 2023, we consummated a registered direct financing pursuant to which we sold an aggregate of 2, 991, 027 shares of our common stock and common warrants to purchase up to 2, 991, 027 shares of our common stock. Each share of common stock and accompanying common warrant were sold together at a combined offering price of $ 5. 015 per share and accompanying warrant. Investors have in the past and** could **in the future** experience substantial dilution of ~~your~~ **their** investment as a result of subsequent exercises of the outstanding warrants. ~~As of March 3, 2023, we had up to $ 240. 0 million of our securities available for sale under the 2021 Registration Statement, of which $ 75. 0 million of our common stock are available pursuant to the 2021 Sales Agreement.~~ In addition, as of December 31, ~~2022~~ **2023** , ~~2~~ **885** , **208** ~~843, 416~~ shares of our common stock were issuable upon exercise of stock options outstanding under our stock option plans at a weighted average exercise price of $ ~~12~~ **9** . ~~97~~ **37** per share, **4** ~~2, 171~~ , 128 **, 259** additional shares of common stock were reserved for potential future issuance under our stock

option plan, and an aggregate of ~~25, 455~~ **55, 667** shares of common stock were reserved for potential future issuance under our 2000 Employee Stock Purchase Plan. At December 31, ~~2022~~ **2023**, we had 150, 000, 000 authorized shares of common stock and, as such, we have the ability to issue significantly more shares and options in the future, which would result in substantial dilution to our stockholders, including investors in this offering. Our ability to use net operating losses and certain other tax attributes is uncertain and may be limited Our ability to use our federal and state net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income before the expiration dates of the net operating losses, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use any or all of our net operating losses. In addition, utilization of net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is subject to annual limitations under the " ownership change " provisions of Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the" Internal Revenue Code") and similar state provisions, which may result in the expiration of net operating losses before future utilization. In general, under the Code, if a corporation undergoes an " ownership change, " generally defined as a greater than 50 % change (by value) in its equity ownership over a three- year period, the corporation' s ability to use its pre- change net operating losses and other pre- change tax attributes (such as research and development credit carryforwards) to offset its post- change taxable income or taxes may be limited. Our equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. If an ownership change limitation were to apply, utilization of our net operating losses and tax credit carryforwards could be limited in future periods and a portion of the carryforwards could expire before being available to reduce future income tax liabilities . We are a " smaller reporting..... attention and our Company' s resources . We have broad discretion over the use of our cash and investments, and their investment may not always yield a favorable return Our management has broad discretion over how our cash and investments are made and used. We may from time to time invest in ways with which our stockholders may not agree and that do not yield favorable returns. Our certificate of incorporation, our bylaws and Delaware law contain provisions that could discourage another company from acquiring us Provisions of Delaware law, our certificate of incorporation and bylaws may discourage, delay or prevent a merger or acquisition that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions include: • authorizing the issuance of " blank check " preferred stock without any need for action by stockholders; • providing for a classified board of directors with staggered terms; • requiring supermajority stockholder voting to effect certain amendments to our certificate of incorporation and bylaws; • eliminating the ability of stockholders to call special meetings of stockholders; • prohibiting stockholder action by written consent; and • establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on by stockholders at stockholder meetings. Our bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees Our bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on behalf of our Company, any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of our Company, any action asserting a claim arising pursuant to any provision of the General Corporation Law of Delaware or our Certificate of Incorporation or bylaws or any action asserting a claim governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition. **We are a " smaller reporting company " as defined in the Exchange Act. As a smaller reporting company, we may take advantage of certain of the scaled disclosures available to smaller reporting companies and will be able to take advantage of these scaled disclosures for so long as (i) our voting and non- voting common stock held by non- affiliates is less than $ 250 million measured on the last business day of our second fiscal quarter, or (ii) our annual revenue is less than $ 100 million during the most recently completed fiscal year and our voting and non- voting common stock held by non- affiliates is less than $ 700 million measured on the last business day of our second fiscal quarter. To the extent we take advantage of any reduced disclosure obligations, it may make it harder for investors to analyze our Company' s results of operations and financial prospectus in comparison with other public companies. 63**