Risk Factors Comparison 2024-02-28 to 2023-03-01 Form: 10-K

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In evaluating our business, you should carefully consider the following risks in addition to the other information in this report. Any of the following risks could materially and adversely affect our business, results of operations, financial condition or your investment in our securities, and many are beyond our control. The risks and uncertainties described below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also adversely affect our business. Risks Specific to our Company in connection with our Research and Development Activities **The regulatory approval process is expensive,** time- consuming and uncertain and may prevent our partners or us from obtaining approvals to commercialize some or all of our drug candidates ~~,including aficamten and omecamtiv mecarbil~~ .The research,testing,manufacturing,selling and marketing of drugs are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries,and regulations differ from country to country.Neither we nor our partners are permitted to market our potential drugs in the United States until we receive approval of an NDA from the FDA.Neither we nor our partners have ~~ever~~ received NDA or other marketing approval for any of our drug candidates.Obtaining NDA approval is a lengthy,expensive and uncertain process.In addition,failure to comply with FDA and other applicable foreign and U.S.regulatory requirements may subject us to administrative or judicially imposed sanctions.These include warning letters,civil and criminal penalties,injunctions,product seizure or detention,product recalls,total or partial suspension of production,and refusal to approve pending NDAs or supplements to approved NDAs. ~~Although we have announced positive results from SEQUOIA- HCM for aficamten and GALACTIC- HF for omecamtiv mecarbil,regulatory~~ **Regulatory** approval of an NDA or NDA supplement is never guaranteed,and the approval process typically takes several years and is extremely expensive.For example,our NDA for omecamtiv mecarbil for the treatment of HFrEF resulted in a CRL notwithstanding the fact that **the** GALACTIC- HF **clinical trial of over 8,000 patients** met its primary efficacy endpoint.The FDA and foreign regulatory agencies also have substantial discretion in the drug approval process,and the guidance and advice issued by such agencies is subject to change at any time.Despite the time and efforts exerted,failure can occur at any stage,and we may encounter problems that cause us to abandon clinical trials or to repeat or perform additional preclinical testing and clinical trials.For example,the CRL we received from FDA in connection with our NDA for omecamtiv mecarbil stated that results from an additional clinical trial of omecamtiv mecarbil are required to establish substantial evidence of effectiveness for the treatment of HFrEF,with benefits that outweigh the risks.The number and focus of preclinical studies and clinical trials that will be required for approval by the FDA and foreign regulatory agencies varies depending on the drug candidate,the disease or condition that the drug candidate is designed to address,and the regulations applicable to any particular drug candidate.In addition,the FDA may require that a proposed REMS be submitted as part of an NDA if the FDA determines that it is necessary to ensure that the benefits of the drug outweigh its risks.The FDA and foreign regulatory agencies can delay,limit or deny approval of a drug candidate for many reasons,including,but not limited to:• they might determine that a drug candidate is not safe or effective;• they might not find the data from non- clinical testing and clinical trials sufficient and could request that additional trials be performed;• they might not approve our,our partner' s or the contract manufacturer' s processes or facilities;or • they might change their approval policies or adopt new regulations.Even if we receive regulatory approval to manufacture and sell a drug in a particular regulatory jurisdiction,other jurisdictions' regulatory authorities may not approve that drug for manufacture and sale.Moreover,the refusal of one regulatory authority to approve one of our drug candidates may influence the decision- making of another regulatory authority in a different jurisdiction in a manner that is adverse to us.For example,FDA' s recent CRL in response to our NDA for omecamtiv mecarbil may influence EMA to decline to approve our MAA for omecamtiv mecarbil in the E.U.or other regulatory authorities in other jurisdictions to decline to approve our potential marketing applications for omecamtiv mecarbil in such other jurisdictions.If we or our partners fail to receive and maintain regulatory approval for the sale of any drugs resulting from our drug candidates,it would **significantly harm our business and negatively affect our stock price.** We ~~recently~~ received a CRL from FDA in response to our NDA for omecamtiv mecarbil. The CRL stated that results from an additional clinical trial of omecamtiv mecarbil are required to establish substantial evidence of effectiveness for the treatment of HFrEF, with benefits that outweigh the risks. No assurance can be given that we will be able to address any of the deficiencies noted in the CRL and / or obtain FDA approval of our NDA for omecamtiv mecarbil. On February 28, 2023, we announced that we received a CRL from the FDA' s Division of Cardiology and Nephrology regarding our NDA for omecamtiv mecarbil for the treatment of HFrEF. According to the CRL, GALACTIC- HF is not sufficiently persuasive to establish substantial evidence of effectiveness for reducing the risk of heart failure events and cardiovascular death in adults with chronic heart failure with HFrEF, in lieu of evidence from at least two adequate and well- controlled clinical investigations. In addition, FDA stated that results from an additional clinical trial of omecamtiv mecarbil are required to establish substantial evidence of effectiveness for the treatment of HFrEF, with benefits that outweigh the risks. FDA' s decision to issue a CRL ~~follows~~ **followed** an FDA Cardiovascular and Renal Drugs Advisory Committee' s vote of 8 to 3 in December 2022 that the benefits of omecamtiv mecarbil do not outweigh its risks for the treatment of HFrEF. ~~We expect~~ **No assurance can be given that we will be able** to ~~request~~ **address any of the deficiencies noted in the CRL and / or obtain FDA approval of our NDA for omecamtiv mecarbil. In 2023, we participated in** a **Type A** meeting with FDA in order to understand FDA' s views regarding the CRL and what may be required to support potential approval of omecamtiv mecarbil in the United States ~~.~~ ~~However~~ , ~~we have no plans to conduct an~~ **and** ~~additional clinical trial~~ **subsequently submitted a formal dispute resolution request to FDA, with the objective to appeal the FDA' s conclusion, as stated in the CRL, that substantial evidence of**

effectiveness had not been established to support approval of omecamtiv mecarbil. ~~No assurance can be given~~ **FDA subsequently denied our appeal in November 2023 and reaffirmed its decision in the CRL** that **GALACTIC- HF is** ~~we will be able to address any of the deficiencies noted~~ -- **not** ~~in the CRL and /~~ **sufficiently persuasive to establish substantial evidence of effectiveness** ~~or~~ **for** ~~obtain FDA approval~~ **reducing the risk** of ~~our NDA for omecamtiv mecarbil~~ **heart failure events and cardiovascular death in adults with chronic heart failure with HFrEF, in lieu of evidence from at least two adequate and well- controlled clinical investigations** . Clinical trials may fail to demonstrate the desired safety and efficacy of our drug candidates ~~, including aficamten and reldesemtiv~~ , which could prevent or significantly delay completion of clinical development and regulatory approval. Prior to receiving approval to commercialize any of our drug candidates, we or our partners must adequately demonstrate to the satisfaction of FDA and foreign regulatory authorities that the drug candidate is sufficiently safe and effective with substantial evidence from well- controlled clinical trials. We or our partners will need to demonstrate efficacy in clinical trials for the treatment of specific indications and monitor safety throughout the clinical development process and following approval. None of our drug candidates have yet met the safety and efficacy standards required for regulatory approval for commercialization and they may never do so. For example, the CRL we received on February 28, 2023 in connection to our NDA for omecamtiv mecarbil stated the results of GALACTIC- HF are not sufficiently persuasive to establish substantial evidence of effectiveness for reducing the risk of heart failure events and cardiovascular death in adults with chronic heart failure with HFrEF **, and on March 31, 2023, we announced the discontinuation of COURAGE-ALS, our Phase 3 clinical trial of reldesemtiv in patients with ALS, due to futility** . In addition, for each of our preclinical compounds, we or our partners must adequately demonstrate satisfactory chemistry, formulation, quality, stability and toxicity in order to submit an IND to the FDA, or an equivalent application in foreign jurisdictions, that would allow us to advance that compound into clinical trials. Furthermore, we or our partners may need to submit separate INDs (or foreign equivalent) to different divisions within the FDA (or foreign regulatory authorities) in order to pursue clinical trials in different therapeutic areas. Each new IND (or foreign equivalent) must be reviewed by the new regulatory division before the clinical trial under its jurisdiction can proceed, entailing all the risks of delay inherent to regulatory review. If our or our partners' current or future preclinical studies or clinical trials are unsuccessful, our business will be significantly harmed and our stock price could be negatively affected. All of our drug candidates are prone to the risks of failure inherent in drug development. Preclinical studies may not yield results that would adequately support the filing of an IND (or a foreign equivalent) with respect to our potential drug candidates. Even if the results of preclinical studies for a drug candidate are sufficient to support such a filing, the results of preclinical studies do not necessarily predict the results of clinical trials. As an example, because the physiology of animal species used in preclinical studies may vary substantially from other animal species and from humans, it may be difficult to assess with certainty whether a finding from a study in a particular animal species will result in similar findings in other animal species or in humans. For any of our drug candidates, the results from Phase 1 clinical trials in healthy volunteers and clinical results from Phase 1 and 2 trials in patients are not necessarily indicative of the results of later and larger clinical trials that are necessary to establish whether the drug candidate is safe and effective for the applicable indication. Likewise, interim results from a clinical trial may not be indicative of the final results from that trial, and results from early Phase 2 clinical trials may not be indicative of the results from later clinical trials. In addition, while the clinical trials of our drug candidates are designed based on the available relevant information, such information may not accurately predict what actually occurs during the course of the trial itself, which may have consequences for the conduct of an ongoing clinical trial or for the eventual results of that trial. For example, the number of patients planned to be enrolled in a placebo- controlled clinical trial is determined in part by estimates relating to expected treatment effect and variability about the primary endpoint. These estimates are based upon earlier non- clinical and clinical studies of the drug candidate itself and clinical trials of other drugs thought to have similar effects in a similar patient population. If information gained during the conduct of the trial shows these estimates to be inaccurate, we may elect to adjust the enrollment accordingly, which may cause delays in completing the trial, additional expense or a statistical penalty to apply to the evaluation of the trial results. Furthermore, in view of the uncertainties inherent in drug development, such clinical trials may not be designed with focus on indications, patient populations, dosing regimens, endpoints, safety, efficacy or pharmacokinetic parameters or other variables that will provide the necessary safety or efficacy data to support regulatory approval to commercialize the resulting drugs. Clinical trials of our drug candidates are designed based on guidance or advice from regulatory agencies, which is subject to change during the development of the drug candidate at any time. Such a change in a regulatory agency' s guidance or advice may cause that agency to deem results from trials to be insufficient to support approval of the drug candidate and require further clinical trials of that drug candidate to be conducted. In addition, individual patient responses to the dose administered of a drug may vary in a manner that is difficult to predict. Also, the methods we select to assess particular safety, efficacy or pharmacokinetic parameters may not yield the same statistical precision in estimating our drug candidates' effects as may other methodologies. Even if we believe the data collected from clinical trials of our drug candidates are promising, these data may not be sufficient to support approval by the FDA or foreign regulatory authorities. Non- clinical and clinical data can be interpreted in different ways. Accordingly, the FDA or foreign regulatory authorities could interpret these data in different ways from us or our partners, which could delay, limit or prevent regulatory approval. Furthermore, while planned interim analyses in clinical trials can enable early terminations for futility or for overwhelming efficacy, the timing, which can be based on accrual of events, enrollment or other factors, and the results of such analyses, is unpredictable. Administering any of our drug candidates or potential drug candidates may produce undesirable side effects, also known as adverse events. Toxicities and adverse events observed in preclinical studies for some compounds in a particular research and development program may also occur in preclinical studies or clinical trials of other compounds from the same program. Potential toxicity issues may arise from the effects of the active pharmaceutical ingredient itself or from impurities or degradants that are present in the active pharmaceutical ingredient or could form over time in the formulated drug candidate or the active pharmaceutical ingredient. These toxicities or adverse events could delay or prevent the filing of an IND

(or a foreign equivalent) with respect to our drug candidates or potential drug candidates or cause us, our partners or the FDA or foreign regulatory authorities to modify, suspend or terminate clinical trials with respect to any drug candidate at any time during the development program. Further, the administration of two or more drugs contemporaneously can lead to interactions between them, and our drug candidates may interact with other drugs that trial subjects are taking. If the adverse events are severe or frequent enough to outweigh the potential efficacy of a drug candidate, the FDA or other regulatory authorities could deny approval of that drug candidate for any or all targeted indications. Even if one or more of our drug candidates were approved for sale as drugs, the occurrence of even a limited number of adverse events or toxicities when used in large populations may cause the FDA or foreign regulatory authorities to impose restrictions on, or stop, the further marketing of those drugs. Indications of potential adverse events or toxicities which do not seem significant during the course of clinical trials may later turn out to actually constitute serious adverse events or toxicities when a drug is used in large populations or for extended periods of time. We have observed certain adverse events in the clinical trials conducted with our drug candidates. Moreover, clinical trials of ~~reldesemtiv and aficamten~~ **our drug candidates** enroll patients who typically suffer from serious diseases which put them at increased risk of death. These patients may die while receiving our drug candidates. In such circumstances, it may not be possible to exclude with certainty a causal relationship to our drug candidate, even though the responsible clinical investigator may view such an event as not study drug- related. Any failure or significant delay in completing preclinical studies or clinical trials for our drug candidates, or in receiving and maintaining regulatory approval for the sale of any resulting drugs, may significantly harm our business and negatively affect our stock price. The regulatory approval process is expensive,..... and negatively affect our stock price. Our clinical trials **, including FOREST- HCM, MAPLE- HCM and ACACIA- HCM,** are expensive, time- consuming and may be subject to delay. Clinical trials are subject to rigorous regulatory requirements and are very expensive, difficult and time- consuming to design and implement. The length of time and number of trial sites and patients required for clinical trials vary substantially based on the type, complexity, novelty, intended use of the drug candidate and safety concerns. Clinical trials of our current drug candidates can each continue for several more years. However, the clinical trials for all or any of our drug candidates may take significantly longer to complete. In addition, as is the case for omecamtiv mecarbil given the CRL requirement to perform an additional Phase 3 clinical trial, the time and expense associated with an additional clinical trial may limit the commercial returns given the eventual loss of market exclusivity. The commencement and completion of our or our partners' clinical trials could be delayed or prevented by many factors, including, but not limited to: • delays in obtaining, or inability to obtain, regulatory or other approvals to commence and conduct clinical trials in the manner we or our partners deem necessary for the appropriate and timely development of our drug candidates and commercialization of any resulting drugs; • delays in identifying and reaching agreement, or inability to identify and reach agreement, on acceptable terms, with prospective clinical trial sites and other entities involved in the conduct of our or our partners' clinical trials; • delays or additional costs in developing, or inability to develop, appropriate formulations of our drug candidates for clinical trial use; • slower than expected rates of patient recruitment and enrollment; • for those drug candidates that are the subject of a strategic alliance, delays in reaching agreement with our partner as to appropriate development strategies; • a regulatory authority may require changes to a protocol for a clinical trial that then may require approval from regulatory agencies in other jurisdictions where the trial is being conducted; • a regulatory authority in one jurisdiction may not accept a clinical trial design that is acceptable in another jurisdiction; • an IRB or its foreign equivalent may require changes to a protocol that then require approval from regulatory agencies and other IRBs and their foreign equivalents, or regulatory authorities may require changes to a protocol that then require approval from the IRBs or their foreign equivalents; • for clinical trials conducted in foreign countries, the time and resources required to identify, interpret and comply with foreign regulatory requirements or changes in those requirements, and political instability or natural disasters occurring in those countries; • lack of effectiveness of our drug candidates during clinical trials; • unforeseen safety issues; • inadequate supply, or delays in the manufacture or supply, of clinical trial materials; • uncertain dosing issues; • failure by us, our partners, or clinical research organizations, investigators or site personnel engaged by us or our partners to comply with good clinical practices and other applicable laws and regulations, including those concerning informed consent; • inability or unwillingness of investigators or their staffs to follow clinical protocols; • failure by our clinical research organizations, clinical manufacturing organizations and other third parties supporting our or our partners' clinical trials to fulfill their obligations; • inability to monitor patients adequately during or after treatment; • introduction of new therapies or changes in standards of practice or regulatory guidance that render our drug candidates or their clinical trial endpoints obsolete; and • results from non- clinical studies that may adversely impact the timing or further development of our drug candidates. We do not know whether planned clinical trials will begin on time, or whether planned or currently ongoing clinical trials will need to be restructured or will be completed on schedule, if at all. Significant delays in clinical trials will impede our ability to commercialize our drug candidates and generate revenue and could significantly increase our development costs. If we encounter difficulties enrolling patients in our clinical trials, including ~~COURAGE~~ **FOREST** ~~ALS~~ **HCM, MAPLE- HCM** and ~~SEQUOIA~~ **ACACIA** - HCM, our clinical development activities could be delayed or otherwise adversely affected. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in clinical trials for a variety of reasons. The enrollment of patients depends on many factors, including: • the patient eligibility criteria defined in the protocol; • the size of the patient population required for analysis of the trial' s primary endpoints; • the proximity of patients to study sites; • the design of the trial; • the ability to recruit clinical trial investigators with the appropriate competencies and experience; • clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies or clinical trials, including any new drugs that may be approved for the indications we are investigating or clinical trial results; • the ability to obtain and maintain patient consents; • the risk that patients enrolled in clinical trials will drop out of the trials before completion ~~; • the effects of the COVID- 19 pandemic, including governmental responses and restrictions on movement and the ability of patients to visit~~

~~clinical trial sites and practicability and / or availability of virtual and / or home healthcare visits~~. In addition, our and our partners' clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our and our partners' product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our or our partners' trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our or our partners' clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site. Delays in patient enrollment may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these trials and adversely affect our and our partners' ability to advance the development of product candidates. The ~~COVID- 19 pandemic continues to adversely impact our business and could materially and adversely affect our operations, as well as the businesses or operations of our or our partners, manufacturers, CROs or other third parties with whom we or our partners conduct business. Disease outbreaks and epidemics in regions where we, our partners or other third parties on which we rely have manufacturing facilities, clinical trial sites or other important operations or pandemics such as the COVID- 19 pandemic could adversely affect our business, including by causing significant disruptions in our operations and / or in the operations of third- party manufacturers and CROs upon whom we rely. For example, the COVID- 19 pandemic has presented a substantial public health and economic challenge around the world and is affecting employees, patients, communities and business operations, as well as the U. S. economy and financial markets. In this regard, the COVID- 19 pandemic and government measures taken in response have had a significant impact, both direct and indirect, on business and commerce, as significant reductions in business- related activities have occurred, supply chains have been disrupted and manufacturing and clinical development activities have been curtailed or suspended. In addition, our clinical trials or those conducted by our partners may continue to be adversely affected by the COVID- 19 pandemic. For example, although we do not believe it will impact our ability to fully enroll SEQUOIA- HCM in a timely fashion, due to the current COVID- 19 outbreak in China, enrollment of patients in SEQUOIA- HCM in China has been adversely affected. Clinical site initiation, conduct, and patient enrollment has been and may continue to be delayed due to prioritization of medical resources toward the COVID- 19 pandemic and restrictions on the ability to travel. It may not be possible to carry out some aspects of clinical trial protocols if quarantines or other restrictions impede patient movement or interrupt healthcare services. It may be necessary to suspend enrollment at some or all clinical trial sites to comply with shelter in place orders, and to reduce the risk to patients, their caretakers, and healthcare providers from contracting COVID- 19. Patients may refuse home healthcare visits, particularly in medically vulnerable patient populations. Similarly, principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID- 19 but also may be pulled into clinical care and away from clinical research, may adversely impact our or our partner' s clinical trial operations. Further, our clinical trial patients who contract COVID- 19 may (i) experience unexpected adverse medical events that could be wrongfully attributable to our investigational drugs, and (ii) experience endpoint events because of COVID- 19 that could confound the interpretation of data and results relating to our investigational drugs arising from our clinical trials. Other key clinical trial activities, such as clinical trial site data monitoring and site inspections, may also be adversely affected due to limitations on travel imposed or recommended by governmental authorities, which may impact the integrity of subject data and clinical study endpoints. Finally, disruptions in our supply chain due to loss of the ability of sites to dispense study drug, travel and import / export restrictions or lack of raw materials may result in an interruption, or delays in receiving, supplies of our drug candidates from our contract manufacturing organizations or study sites, which in turn may also adversely affect our clinical trials. The spread of COVID- 19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by, and the duration of, COVID- 19 may be difficult to assess or predict, a continued pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID- 19 could materially affect our business and the value of our common stock. The ultimate impact of the COVID- 19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID- 19 situation closely. The~~ failure to successfully develop, ~~validate~~ **manufacture** and obtain regulatory clearance or approval of an antibody- based immunoassay for ~~plasma~~ **blood** concentrations of omecamtiv mecarbil **by Microgenics Corporation, a subsidiary of Thermo Fisher,** could harm our development and commercialization strategy for omecamtiv mecarbil in ~~the United States~~ **key markets. In addition, if required by FDA and / or EMA as part of any approved label for omecamtiv mecarbil, we will be dependent on Microgenics to manufacture and commercialize such an immunoassay in sufficient quantities in all key markets in which we may seek to commercialize omecamtiv mecarbil**. In connection with our NDA **and our MAA** for omecamtiv mecarbil, FDA **and / or EMA** may ~~as a condition to approval~~ require that patients treated with omecamtiv mecarbil have their blood monitored during titration for concentrations of the drug in order to ensure optimized dosing that maximizes benefits without undue increased risk. **We have recently contracted** ~~To address such a requirement, we would need to enter into an agreement~~ with **Microgenics Corporation,** a ~~suitable partner~~ **subsidiary of Thermo Fisher,** to develop and ~~operationalize~~ **eventually commercialize** an antibody- based immunoassay ~~, and no assurance can be given that we will identify a suitable partner with the necessary expertise and capabilities, agree to contractual terms that are advantageous to us, or~~ **for blood concentrations** ~~that such partner will in fact commercialize the test in a manner that is supportive~~ of ~~our development and commercialization efforts for~~ omecamtiv mecarbil. **The** ~~Moreover, even if we were able to identify such a partner and to reach an acceptable agreement therewith, the~~ development **, manufacture and regulatory approval** of an antibody- based immunoassay **, however,** may be complex ~~from an~~ **and** ~~operational and regulatory perspective~~ **/ or time consuming**. Such an immunoassay could require regulatory clearance by FDA as a companion diagnostic device **or similar regulatory clearance by EMA,** and **there is** no

assurance that such regulatory clearance will be obtained. ~~The failure~~ **In addition, if required by FDA and / or EMA as part of any approved label for omecamtiv mecarbil, we will be dependent on Microgenics Corporation** to successfully **manufacture** ~~develop, validate and obtain regulatory clearance or approval of an~~ **and** ~~antibody based~~ **commercialize its** immunoassay ~~for plasma concentrations~~ **in sufficient quantities in all key markets in which we may seek to commercialize omecamtiv mecarbil, failing which, our potential sales** of omecamtiv mecarbil could be **materially adversely affected** ~~required by EMA for approval of our MAA in the E. U. and as a result could delay our development and commercialization strategy for omecamtiv mecarbil in the E. U. and other countries of the EEA. EMA may require the use of an antibody- based immunoassay that is comparable to the one developed by Microgenics Corporation, an affiliate of Thermo Fisher, and utilized in GALACTIC- HF as a condition to approval of our MAA for omecamtiv mecarbil. We currently have no agreement in place with Microgenics Corporation or any other company to develop or commercialize an immunoassay that is comparable to the one utilized in GALACTIC- HF. No assurance can be given that we will identify a suitable partner with the necessary expertise and capabilities, agree to contractual terms that are advantageous to us, or that such partner will in fact commercialize the test in a manner that is supportive of our commercialization efforts for omecamtiv mecarbil in the European Union and the other members of the EEA. Moreover, even if we were able to identify such a partner and to reach an acceptable agreement therewith, the development of an antibody- based immunoassay may be complex from an operational and regulatory perspective. Such an immunoassay would require regulatory clearances by the appropriate regulatory authorities in Europe and no assurance that such regulatory clearances will be obtained~~ . We depend on CROs to conduct our clinical trials **as well as other third parties to manufacture drug candidates for use in clinical trials** and **we** have limited control over their performance. If these CROs do not successfully carry out their contractual duties or meet expected deadlines, or if we lose any of our CROs, we may not be able to obtain regulatory approval for or commercialize our product candidates on a timely basis, if at all. We have used and intend to continue to use a limited number of CROs within and outside of the United States to conduct clinical trials of our drug candidates and related activities. We do not have control over many aspects of our CROs' activities, and cannot fully control the amount, timing or quality of resources that they devote to our programs. CROs may not assign as high a priority to our programs or pursue them as diligently as we would if we were undertaking these programs ourselves. The activities conducted by our CROs therefore may not be completed on schedule or in a satisfactory manner. CROs may also give higher priority to relationships with our competitors and potential competitors than to their relationships with us. Outside of the United States, we are particularly dependent on our CROs' expertise in communicating with clinical trial sites and regulatory authorities and ensuring that our clinical trials and related activities and regulatory filings comply with applicable laws. Our CROs' failure to carry out development activities on our behalf as agreed and in accordance with our and the FDA' s or other regulatory agencies' requirements and applicable U. S. and foreign laws, or our failure to properly coordinate and manage these activities, could increase the cost of our operations and delay or prevent the development, approval and commercialization of our drug candidates. In addition, if a CRO fails to perform as agreed, our ability to collect damages may be contractually limited. If we fail to effectively manage the CROs carrying out the development of our drug candidates or if our CROs fail to perform as agreed, the commercialization of our drug candidates will be delayed or prevented. In many cases, our CROs have the right to terminate their agreements with us in the event of an uncured material breach. Identifying, qualifying and managing performance of third- party service providers can be difficult, time consuming and cause delays in our development programs. In addition, there is a natural transition period when a new CRO commences work and the new CRO may not provide the same type or level of services as the original provider. If any of our relationships with our third- party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so timely or on commercially reasonable terms. The mechanisms of action of certain of our drug candidates are unproven, and we do not know whether we will be able to develop any drug of commercial value. We have discovered and develop drug candidates that have what we believe are novel mechanisms of action directed against cytoskeletal targets. The results we have seen for our compounds in preclinical models may not translate into similar results in humans, and results of early clinical trials in humans may not be predictive of the results of larger clinical trials that may later be conducted with our drug candidates. Even if we are successful in developing and receiving regulatory approval for a drug candidate for the treatment of a particular disease, we cannot be certain that it will be accepted by prescribers or be reimbursed by insurers or that we will also be able to develop and receive regulatory approval for that or other drug candidates for the treatment of other diseases. If we or our partners are unable to successfully develop and commercialize our drug candidates, our business will be materially harmed. Moreover, in the event any of our competitors were to develop their own drug candidates that have a similar mechanism of action to any of our drug candidates and compounds, any efficacy or safety concerns identified during the development of such similar drug candidates may have an adverse impact on the development of our own drug candidates. For example, if a competitor' s drug candidate having a similar mechanism of action as any of our own drug candidates is shown in clinical trials to give rise to serious safety concerns or have poor efficacy when administered to the target patient population, the FDA or other regulatory bodies may subject our drug candidates to increased scrutiny, leading to additional delays in development and potentially decreasing the chance of ultimate approval of our own drug candidates. We have been granted orphan designation by the FDA ~~and EMA for reldesemtiv for the potential treatment ALS and orphan designation by the FDA~~ for aficamten for the potential treatment of symptomatic HCM; however, there can be no guarantee that we will receive ~~orphan~~ approval for ~~reldesemtiv or~~ aficamten **for this indication** , nor that we will be able to prevent third parties from developing and commercializing products that are competitive to ~~reldesemtiv or~~ aficamten. We have been granted orphan drug designation in the U. S. by the FDA for ~~reldesemtiv for the potential treatment of ALS and for~~ aficamten for the ~~potential~~ treatment of symptomatic HCM. In the U. S., upon approval from the FDA of an NDA, products granted orphan drug designation are generally provided with seven years of marketing exclusivity in the U. S., meaning the FDA will generally not approve applications for other product candidates that contain the same active ingredient for the same orphan indication. Even if we are the first to obtain approval of an orphan product and are granted such exclusivity in the U. S., there are limited

circumstances under which a later competitor product may be approved for the same indication during the seven- year period of marketing exclusivity, such as if the later product is shown to be clinically superior to our product or due to an inability to assure a sufficient quantity of the orphan drug. ~~EMA has granted orphan medicinal product designation to reldesemtiv for the potential treatment of SMA and the potential treatment of ALS.~~ Orphan medicinal product status in the E. U. can provide up to 10 years of marketing exclusivity, meaning that another application for marketing authorization of a later similar medicinal product for the same therapeutic indication will generally not be approved in the E. U. Although we may have drug candidates that may obtain orphan drug exclusivity in Europe, the orphan approval and associated exclusivity period may be modified for several reasons, including a significant change to the orphan medicinal product designations or approval criteria after- market authorization of the orphan product (e. g., product profitability exceeds the criteria for orphan drug designation), problems with the production or supply of the orphan drug or a competitor drug, although similar, is safer, more effective or otherwise clinically superior than the initial orphan drug. We are not guaranteed to maintain orphan status ~~for reldesemtiv~~ **from the FDA** ~~or~~ **for** aficamten or to receive orphan status for ~~reldesemtiv or~~ aficamten for any other indication or for any of our other drug candidates for any indication. We are not guaranteed to be granted orphan designation in the E. U. for aficamten by the EMA. If our drug candidates that are granted orphan status were to lose their status as orphan drugs or the marketing exclusivity provided for them in the U. S. or the E. U., our business and results of operations could be materially adversely affected. While orphan status for any of our products, if granted or maintained, would provide market exclusivity in the U. S. and the E. U. for the time periods specified above, we would not be able to exclude other companies from manufacturing and / or selling products using the same active ingredient for the same indication beyond the exclusivity period applicable to our product on the basis of orphan drug status. Moreover, we cannot guarantee that another company will not receive approval before we do of an orphan drug application in the U. S. or the E. U. for a product candidate that has the same active ingredient or is a similar medicinal product for the same indication as any of our drug candidates for which we plan to file for orphan designation and status. If that were to happen, our orphan drug applications for our drug candidate for that indication may not be approved until the competing company' s period of exclusivity has expired in the U. S. or the E. U., as applicable. Further, application of the orphan drug regulations in the U. S. and Europe is uncertain, and we cannot predict how the respective regulatory bodies will interpret and apply the regulations to our or our competitors' products. We have been granted Breakthrough Therapy Designation for aficamten by the FDA and we may seek additional special designations from regulatory authorities to expedite the review and approval process for our product candidates. However, these designations may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval. We have been granted Breakthrough Therapy Designation for aficamten for oHCM by the FDA and may seek these and / or additional special designations from regulatory authorities to expedite the review and approval process for our product candidates. A breakthrough therapy is defined as a drug candidate that is intended, alone or in combination with one or more other products, to treat a serious or life- threatening disease or condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically important endpoints, such as substantial treatment effects observed early in clinical development. For products that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drug candidates designated as breakthrough therapies by the FDA can also be eligible for accelerated approval. If a drug candidate is intended for the treatment of a serious or life- threatening condition and the product demonstrates the potential to address unmet medical needs for this condition, the drug candidate sponsor may apply for Fast Track Designation. Fast Track Designation is an FDA process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose of the program is to make important new drugs available to the patient earlier. Filling an unmet medical need is defined as providing a therapy where none exists or providing a potential improvement upon the current standard of care. Once a drug candidate receives Fast Track Designation, early and frequent communication between the FDA and the sponsor is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients. The FDA has broad discretion whether or not to grant these designations, so even if we believe a particular drug candidate is eligible for a particular designation, we cannot assure you that the FDA would decide to grant it. Accordingly, even if we believe one of our drug candidates meets the criteria for a designation, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a particular designation for a product candidate may not result in a faster development process, review or approval compared to drug candidates considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our drug candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification and rescind the breakthrough designation. Further, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from a clinical development program. If we are unable to maintain any existing Breakthrough Therapy Designation or Fast Track Designation or fail to secure such designation for any additional product candidates, this would have an adverse impact on our development timelines and our ability to obtain approval for and commercialize our product candidates. Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed or commercialized in a timely manner, which could negatively impact our business. The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at

the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and / or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U. S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Separately, in response to the global COVID- 19 pandemic, the FDA had a period during which manufacturing inspections were not conducted, leading to delay, and has resumed on- site inspections of domestic manufacturing facilities subject to a risk- based prioritization system. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Risks Specific to our Company in connection with our Commercial Operations Our competitors may develop drugs that are less expensive, safer and / or more effective than ours, which may diminish or eliminate the commercial success of any drugs that we may commercialize. We compete with companies that have developed drugs or are developing drug candidates for cardiovascular diseases, diseases and conditions associated with muscle weakness or wasting and other diseases for which our drug candidates may be useful treatments. Our competitors may: • develop drug candidates and market drugs that are less expensive or more effective than our future drugs; • commercialize competing drugs before we or our partners can launch any drugs developed from our drug candidates; • hold or obtain proprietary rights that could prevent us from commercializing our products; • initiate or withstand substantial price competition more successfully than we can; • more successfully recruit skilled scientific workers and management from the limited pool of available talent; • more effectively negotiate third- party licenses and strategic alliances; • take advantage of acquisition or other opportunities more readily than we can; • develop drug candidates and market drugs that increase the levels of safety or efficacy that our drug candidates will need to show in order to obtain regulatory approval; or • introduce therapies or market drugs that render the market opportunity for our potential drugs obsolete. We will compete for market share against large pharmaceutical and biotechnology companies and smaller companies that are collaborating with larger pharmaceutical companies, new companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors, either alone or together with their partners, may develop new drug candidates that will compete with ours. Many of these competitors have larger research and development programs or substantially greater financial resources than we do. Our competitors may also have significantly greater experience in: • developing drug candidates; • undertaking preclinical testing and clinical trials; • building relationships with key customers and opinion- leading physicians; • obtaining and maintaining FDA and other regulatory approvals of drug candidates; • formulating and manufacturing drugs; and • launching, marketing and selling drugs. If our competitors market drugs that are less expensive, safer and / or more efficacious than our potential drugs, or that reach the market sooner than our potential drugs, we may not achieve commercial success. In addition, the life sciences industry is characterized by rapid technological change. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Our competitors may render our technologies obsolete by improving existing technological approaches or developing new or different approaches, potentially eliminating the advantages in our drug discovery process that we believe we derive from our research approach and proprietary technologies. Even if our drug candidates are approved, we may experience difficulties or delays in achieving market access, reimbursement and favorable drug pricing for our drug products. We currently have limited interactions and relationships with payors. Over time, we anticipate that our drugs will be adopted by our patients as indicated by the labels once they are approved by regulatory authorities. To achieve this adoption, our drugs will need to be covered and listed in formularies of major pharmacy benefit managers and payors in the U. S. These major pharmacy benefit managers and payors include Medicare, Medicaid, VA, DoD, TriCare, and other commercial payors with whom we have had limited interactions. The process to achieve coverage with pharmacy benefit managers and payors can be time consuming, is not guaranteed and if achieved can impact profitability given the level of rebates often required. Specifically in relation to **aficamten and** omecamtiv mecarbil, even if such drug ~~candidate~~ **candidates** ~~is~~ **are** ultimately approved by the FDA or other regulatory authorities for commercialization, ~~it~~ **they** may not become a guideline- directed medical therapy for **oHCM** ~~heart failure~~ or ~~it~~ **HFrEF respectively or they** may not reach such status in a timely manner upon commercialization, which may adversely impact its sales prospects. Furthermore, we assume omecamtiv mecarbil will have a disproportionally larger share of Medicare patients relative to commercial and other payors. Overall coverage could be delayed given Medicare' s defined bid timelines for inclusion in the Medicare Part D formulary. In addition, the rebate levels we may have to offer to pharmacy benefit managers and payors to be included in their formularies may also impact the profitability of omecamtiv mecarbil. Moreover, pricing of our drug candidates, if approved by the FDA or other regulatory authorities for commercialization, may be impacted by cost- effectiveness and economic analyses by a Health Technology Assessment organization such as the Institute for Clinical and Economic Review, or ICER, an independent non- profit research institute that produces reports analyzing the evidence underlying the effectiveness and value of drugs and other medicinal services. ICER assessments and recommended pricing based on cost- effectiveness may affect our ability to obtain favorable pricing terms with Medicare, Medicaid, VA, DoD, TriCare, and other commercial payors. For example, in November 2021, ICER published its final evidence report and policy recommendations related to Camzyostm (mavacamten), a small molecule myosin inhibitor ~~being~~ developed **formerly by MyoKardia, Inc. and commercialized** by Bristol- Myers Squibb Company ~~(formerly by MyoKardia, Inc.)~~ that has a similar mechanism of action to aficamten. The report concluded that a majority of contributing panelists found that current evidence was not adequate to demonstrate a net health benefit for Camzyostm (mavacamten) added to background therapy when compared to background therapy alone or a net health benefit of Camzyostm (mavacamten) when compared to disopyramide. Moreover, ICER' s final report concluded that modeling short- term clinical benefits of Camzyostm (mavacamten) over a longer time period produces a health- benefit price benchmark index

for Camzyostm (mavacamten) between $ 12, 000- $ 15, 000 per year, significantly lower than ~~the $ 94, 870 annual list price at launch that~~ Bristol- Myers Squibb Company ~~has indicated~~ **' s current annual list price in the U. S** . Whilst not binding on Medicare, Medicaid, VA, DoD, TriCare, and other commercial payors, or indicative of the net health benefits, ICER could conclude for aficamten a similar conclusion that could adversely impact our ability to obtain favorable pricing **and / or reimbursement** . The commercial success of our products depends on the availability and sufficiency of third - party payor coverage and reimbursement. Patients in the United States and elsewhere generally rely on third - party payors to reimburse part or all of the costs associated with their prescription drugs. Accordingly, market acceptance of our products is dependent on the extent to which third - party coverage and reimbursement is available from government health administration authorities (including in connection with government healthcare programs, such as Medicare and Medicaid in the United States), private healthcare insurers and other healthcare funding organizations. Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. Even if we obtain coverage for a given drug product, the timeframe from approval to coverage could be lengthy, inadequate, and / or the associated reimbursement rate may not be adequate to cover our costs, including research, development, intellectual property, manufacture, sale and distribution expenses, or may require co - payments that patients find unacceptably high. Coverage and reimbursement policies for drug products can differ significantly from payor to payor as there is no uniform policy of coverage and reimbursement for drug products among third - party payors in the United States. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time - consuming and costly which will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage or adequate reimbursement will be obtained. It is difficult to predict at this time what third- party will decide with respect to coverage and reimbursement for our products. Coverage policies and third party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. In addition, there is significant uncertainty regarding the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost- effectiveness of our products. If third- party payors do not consider our products to be cost- effective compared to other therapies, the payors may not cover our products as a benefit under their plans, or if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis. **Additionally, we or our partners may develop companion diagnostic tests for use with our product candidates. Companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical products, will apply to companion diagnostics.** We expect that increased emphasis on cost containment measures in the United States by third - party payors to continue and will place pressure on pharmaceutical pricing and coverage. Coverage policies and third- party reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. If we are unable to obtain and maintain sufficient third - party coverage and adequate reimbursement for our products, the commercial success of our drug products may be greatly hindered and our financial condition and results of operations may be materially and adversely affected. We have no manufacturing ~~capacity~~ **capabilities** and depend on contract manufacturers to produce our clinical trial materials, including our drug candidates, and will have continued reliance on contract manufacturers for the development and commercialization of our potential drugs. We do not currently operate manufacturing facilities for clinical or commercial production of our drug candidates and rely on CMOs for the manufacture of finished drug product and active pharmaceutical ingredient. We have limited experience in drug formulation and manufacturing, and we lack the resources and the capabilities to manufacture any of our drug candidates on a clinical or commercial scale. In addition, under the Ji Xing Agreements, we have committed to providing Ji Xing with supply of aficamten and omecamtiv mecarbil for development and commercialization of aficamten and omecamtiv mecarbil in China and Taiwan, which we will have to source from our contract manufacturers. We expect to rely on contract manufacturers to supply all future drug candidates for which we conduct development, as well as other materials required to conduct our clinical trials, and to fulfil our obligations under the Ji Xing Agreements. If any of our existing or future contract manufacturers fail to perform satisfactorily, it could delay development or regulatory approval of our drug candidates or commercialization of our drugs, producing additional losses and depriving us of potential product revenues, and also lead to our breach of one or both of the Ji Xing Agreements, giving rise to the ability to terminate such agreements and other adverse consequences as stipulated in the Ji Xing Agreements. In addition, if a contract manufacturer fails to perform as agreed, our ability to collect damages may be contractually limited. Our drug candidates require precise high- quality manufacturing. The failure to achieve and maintain high manufacturing standards, including failure to detect or control anticipated or unanticipated manufacturing errors or the frequent occurrence of such errors, could result in patient injury or death, discontinuance or delay of ongoing or planned clinical trials, delays or failures in product testing or delivery, cost overruns, product recalls or withdrawals and other problems that could seriously hurt our business. Contract drug manufacturers often encounter difficulties involving production yields, quality control and quality assurance and shortages of qualified personnel. These manufacturers are subject to stringent regulatory requirements, including the FDA' s current good manufacturing practices regulations and similar foreign laws and standards. Each contract manufacturer must pass a pre-approval inspection before we can obtain marketing approval for any of our drug candidates and following approval will be subject to ongoing periodic unannounced inspections by the FDA, the U. S. Drug Enforcement Agency and other regulatory agencies, to ensure strict compliance with current good manufacturing practices and other applicable government regulations and corresponding foreign laws and standards. We seek to ensure that our contract manufacturers comply fully with all applicable regulations, laws and standards. However, we do not have control over our contract manufacturers' compliance with

these regulations, laws and standards. If one of our contract manufacturers fails to pass its pre- approval inspection or maintain ongoing compliance at any time, the production of our drug candidates could be interrupted, resulting in delays or discontinuance of our clinical trials, additional costs and potentially lost revenues. In addition, failure of any third- party manufacturers or us to comply with applicable regulations, including pre- or post- approval inspections and the current good manufacturing practice requirements of the FDA or other comparable regulatory agencies, could result in sanctions being imposed on us. These sanctions could include fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delay, suspension or withdrawal of approvals, license revocation, product seizures or recalls, operational restrictions and criminal prosecutions, any of which could significantly and adversely affect our business. In addition, our existing and future contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to successfully produce, store and distribute our drug candidates. If a natural disaster, business failure, strike or other difficulty occurs, we may be unable to replace these contract manufacturers in a timely or cost- effective manner and the production of our drug candidates would be interrupted, resulting in delays, loss of customers and additional costs. Switching manufacturers or manufacturing sites would be difficult and time- consuming because the number of potential manufacturers is limited. In addition, before a drug from any replacement manufacturer or manufacturing site can be commercialized, the FDA and, in some cases, foreign regulatory agencies, must approve that site. These approvals would require regulatory testing and compliance inspections. A new manufacturer or manufacturing site also would have to be educated in, or develop substantially equivalent processes for, production of our drugs and drug candidates. It may be difficult or impossible to transfer certain elements of a manufacturing process to a new manufacturer or for us to find a replacement manufacturer on acceptable terms quickly, or at all, either of which would delay or prevent our ability to develop drug candidates and commercialize any resulting drugs. We may not be able to successfully manufacture our drug candidates in sufficient quality and quantity, which would delay or prevent us from developing our drug candidates and commercializing ~~resulting~~ approved ~~drugs~~ **drug products**, if any. To date, our drug candidates have been manufactured in quantities adequate for preclinical studies and early through late- stage clinical trials. In order to conduct large scale clinical trials for a drug candidate and for commercialization of the resulting drug if that drug candidate is approved for sale, we will need to manufacture some drug candidates in larger quantities. We may not be able to successfully repeat or increase the manufacturing capacity for any of our drug candidates, whether in collaboration with third- party manufacturers or on our own, in a timely or cost- effective manner or at all. If a contract manufacturer makes improvements in the manufacturing process for our drug candidates, we may not own, or may have to share, the intellectual property rights to those improvements. Significant changes or scale- up of manufacturing may require additional validation studies, which are costly and which regulatory authorities must review and approve. In addition, quality issues may arise during those changes or scale- up activities because of the inherent properties of a drug candidate itself or of a drug candidate in combination with other components added during the manufacturing and packaging process, or during shipping and storage of the finished product or active pharmaceutical ingredients. If we are unable to successfully manufacture of any of our drug candidates in sufficient quality and quantity, the development of that drug candidate and regulatory approval or commercial launch for any resulting drugs may be delayed or there may be a shortage in supply, which could significantly harm our business. In addition, data demonstrating the stability of both drug substance and drug product, using the commercial manufacturing process and at commercial scale, are required for marketing applications. Failure to produce drug substance and drug products in a timely manner and obtain stability data could result in delay of submission of marketing applications. If we or our partners receive regulatory approval for our drug candidates, we or they will be subject to ongoing obligations to and continued regulatory review by the FDA and foreign regulatory agencies, and may be subject to additional post- marketing obligations **such as an ETASU or other form of REMS**, all of which may result in significant expense and limit commercialization of our potential drugs. Any regulatory approvals that we or our partners receive for our drug candidates may be subject to limitations on the indicated uses for which the drug may be marketed or require potentially costly post- marketing follow- up studies or compliance with a REMS **. For example, Camzyostm (mavacamten), a small molecule myosin inhibitor developed formerly by MyoKardia, Inc. and commercialized by Bristol- Myers Squibb Company that has a similar mechanism of action to aficamten, is subject to an ETASU REMS, an FDA imposed program designed to reinforce medication use behaviors and actions that support the safe use of certain medication with serious safety concerns to help ensure the benefits of the medication outweigh its risks. The Camzyostm (mavacamten) ETASU REMS program requires, among other things, restrictions and qualifications on pharmacies that dispense the drug and certification, record- keeping and patient counselling obligations on physicians who prescribe the drug. The requirements of an ETASU REMS program may limit the commercial success of a drug due by making it more difficult for physicians to prescribe a drug and patients to obtain and subsequently use a drug. Since aficamten is a small molecule myosin inhibitor with a similar mechanism of action to Camzyostm (mavacamten), it is possible that FDA or other regulatory bodies may condition aficamten' s marketing approval on the implementation of a similar ETASU REMS program to that of Camzyostm (mavacamten)**. In addition, if the FDA or foreign regulatory agencies approves any of our drug candidates, the labeling, packaging, adverse event reporting, storage, advertising, promotion and record- keeping for the drug will be subject to extensive regulatory requirements. The subsequent discovery of previously unknown problems with the drug, including adverse events of unanticipated severity or frequency, or the discovery that adverse events or toxicities observed in preclinical research or clinical trials that were believed to be minor constitute much more serious problems, may result in restrictions on the marketing of the drug or withdrawal of the drug from the market. The FDA and foreign regulatory agencies may change their policies and additional government regulations may be enacted that could prevent or delay regulatory approval of our drug candidates. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are not able to maintain regulatory compliance, we might not be permitted to market

our drugs and our business would suffer. If physicians and patients do not accept our drugs, we may be unable to generate significant revenue, if any. Even if our drug candidates obtain regulatory approval, the resulting drugs, if any, may not gain market acceptance among physicians, healthcare payors, patients and the medical community. Even if the clinical safety and efficacy of drugs developed from our drug candidates are established for purposes of approval, physicians may elect not to recommend these drugs for a variety of reasons including, but not limited to: • introduction of competitive drugs to the market; • clinical safety and efficacy of alternative drugs or treatments; • cost- effectiveness; • availability of coverage and reimbursement from health maintenance organizations and other third- party payors; • convenience and ease of administration; • prevalence and severity of adverse events; • other potential disadvantages relative to alternative treatment methods; or • insufficient patient support; • insufficient marketing and distribution support. If our drugs fail to achieve market acceptance, we may not be able to generate significant revenue and our business would suffer. Risks Specific to our Company in connection with our Intellectual Property Our success depends substantially upon our ability to obtain and maintain intellectual property protection relating to our drug candidates, compounds and research technologies. We own, co- own or hold exclusive licenses to a number of U. S. and foreign patents and patent applications directed to our drug candidates, compounds and research technologies. Our success depends on our ability to obtain patent protection both in the United States and in other countries for our drug candidates, their methods of manufacture and use, and our technologies. Our ability to protect our drug candidates, compounds and technologies from unauthorized or infringing use by third parties depends substantially on our ability to obtain and enforce our patents. If our issued patents and patent applications, if granted, do not adequately describe, enable or otherwise provide coverage of our technologies and drug candidates, we, our licensors or our licensees would not be able to exclude others from developing or commercializing these drug candidates. Furthermore, the degree of future protection of our proprietary rights is uncertain because legal means may not adequately protect our rights or permit us to gain or keep our competitive advantage. If we are unable to obtain and maintain sufficient intellectual property protection for our technologies and drug candidates, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize drug candidates similar or identical to ours, and our ability to successfully commercialize product candidates that we may pursue may be impaired. Obtaining and enforcing biopharmaceutical patents is costly, time consuming and complex, and we may not be able to file and prosecute all necessary or desirable patent applications, or maintain, enforce and license any patents that may issue from such patent applications, at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the rights to patents licensed to third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and the claim scope of these patents, our ability to enforce our existing patents and to obtain and enforce patents that may issue from any pending or future patent applications is uncertain and involves complex legal, scientific and factual questions. The standards which the U. S. Patent and Trademark Office and its foreign counterparts use to grant patents are not always applied predictably or uniformly and are subject to change. To date, no consistent policy has emerged regarding the breadth of claims allowed in biotechnology and pharmaceutical patents. Thus, we cannot be sure that any patents will issue from any pending or future patent applications owned by, co- owned by or licensed to us. Even if patents do issue, we cannot be sure that the claims of these patents will be held valid or enforceable by a court of law, will provide us with any significant protection against competitive products, or will afford us a commercial advantage over competitive products. In particular: • we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications or issued patents; • we or our licensors might not have been the first to file patent applications for the inventions covered by our pending patent applications or issued patents; • others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights; • some or all of our or our licensors' pending patent applications may not result in issued patents or the claims that issue may be narrow in scope and not provide us with competitive advantages; • our and our licensors' issued patents may not provide a basis for commercially viable drugs or therapies or may be challenged and invalidated by third parties; • our or our licensors' patent applications or patents may be subject to interference, post- grant proceedings, derivation, reexamination, inter partes review, opposition or similar legal and administrative proceedings that may result in a reduction in their scope or their loss altogether; • we may not develop additional proprietary technologies or drug candidates that are patentable; or • the patents of others may prevent us or our partners from discovering, developing or commercializing our drug candidates. We may not be able to protect our intellectual property rights throughout the world. Patent protection is afforded on a country- by- country basis. Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. Many companies have encountered significant difficulties in protecting and defending intellectual property rights in foreign jurisdictions. Some of our development efforts are performed in countries outside of the United States through third- party contractors. We may not be able to effectively monitor and assess intellectual property developed by these contractors. We therefore may not be able to effectively protect this intellectual property and could lose potentially valuable intellectual property rights. In addition, the legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective of intellectual property rights as in the United States. Therefore, we may be unable to acquire and protect intellectual property developed by these contractors to the same extent as if these development activities were being conducted in the United States. If we encounter difficulties in protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed. Patent terms may be inadequate to protect our competitive position on our technologies and drug candidates for an adequate amount of time. Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U. S. non-

provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our technologies and drug candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned, co- owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours or our partners. Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non- compliance with these requirements. Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and / or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and / or applications. Non- compliance could result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business. We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property. We rely on intellectual property assignment agreements with our corporate partners, employees, consultants, scientific advisors and other collaborators to grant us ownership of new intellectual property that is developed. These agreements may not result in the effective assignment to us of that intellectual property. As a result, our ownership of key intellectual property could be compromised. We or our licensors may be subject to claims that former employees, collaborators, consultants or other third parties have an interest in our owned, co- 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, collaborators, consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship of our or our licensors' ownership of our owned, co- 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. We are a party to license agreements and may need to obtain additional licenses from others to advance our research and development activities or allow the commercialization of our drug candidates and future drug candidates we may identify and pursue. If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or these agreements are terminated or we otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business. Our licensors might conclude that we have materially breached our obligations under such license agreements and might therefore terminate, or seek to terminate, the license agreements, thereby removing or limiting our ability to develop and commercialize products and technology covered by these license agreements. If our license agreements are terminated, we may be required to cease our development and commercialization of our product candidates. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects. Moreover, disputes may arise regarding intellectual property subject to a licensing agreement. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects. Changes in either the patent laws or their interpretation in the United States or other countries may diminish the value of our intellectual property or our ability to obtain patents. For example, the America Invents Act of 2011 may affect the scope, strength and enforceability of our patent rights in the United States or the nature of proceedings which may be brought by us related to our patent rights in the United States. If one or more products resulting from our drug candidates is approved for sale by the FDA and we do not have adequate intellectual property protection for those products, competitors could duplicate them for approval and sale in the United States without repeating the extensive testing required of us or our partners to obtain FDA approval. Regardless of any patent protection, under current law, an application for a generic version of a new chemical entity cannot be approved until at least five years after the FDA has approved the original product. When that period expires, or if that period is altered, the FDA could approve a generic version of our product regardless of our patent protection. An applicant for a generic version of our product may only be required to conduct a relatively inexpensive study to show that its product is bioequivalent to our product, and may not have to repeat the lengthy and expensive clinical trials that we or our partners conducted to demonstrate that the product is safe and effective. In the absence of adequate patent protection for our products in other countries, competitors may similarly be able to obtain regulatory approval in those countries of generic versions of our products. If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed. We also rely on trade secrets to protect our technology, particularly where we believe patent protection is not appropriate or obtainable. However, trade secrets are often difficult to protect, especially outside of the United States. While we endeavor to use reasonable efforts to protect our trade secrets, our or our partners' employees, consultants, contractors or scientific and other advisors may unintentionally or willfully disclose our information to competitors. In addition, confidentiality agreements, if any, executed by those individuals may not be enforceable

or provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure. We cannot be certain that such agreements have been entered into with all relevant parties, and we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Pursuing a claim that a third party had illegally obtained and was using our trade secrets would be expensive and time- consuming, and the outcome would be unpredictable. Even if we are able to maintain our trade secrets as confidential, if our competitors lawfully obtain or independently develop information equivalent or similar to our trade secrets, our business could be harmed. If we are not able to defend the patent or trade secret protection position of our technologies and drug candidates, then we will not be able to exclude competitors from developing or marketing competing drugs, and we may not generate enough revenue from product sales to justify the cost of development of our drugs or to achieve or maintain profitability. If we are sued for infringing third-party intellectual property rights, it will be costly and time- consuming, and an unfavorable outcome could have a significant adverse effect on our business. Our ability to commercialize drugs depends on our ability to use, manufacture and sell those drugs without infringing the patents or other proprietary rights of third parties. Numerous U. S. and foreign issued patents and pending patent applications owned by third parties exist in the therapeutic areas in which we are developing drug candidates and seeking new potential drug candidates. In addition, because patent applications can take several years to issue, there may be currently pending applications, unknown to us, which could later result in issued patents that our activities with our drug candidates could infringe. There may also be existing patents, unknown to us, that our activities with our drug candidates could infringe. Other future products of ours may be impacted by patents of companies engaged in competitive programs with significantly greater resources. Further development of these products could be impacted by these patents and result in significant legal fees. If a third party claims that our actions infringe its patents or other proprietary rights, we could face a number of issues that could seriously harm our competitive position, including, but not limited to: • infringement and other intellectual property claims that, even if meritless, can be costly and time- consuming to litigate, delay the regulatory approval process and divert management' s attention from our core business operations; • substantial damages for past infringement which we may have to pay if a court determines that our drugs or technologies infringe a third party' s patent or other proprietary rights; • a court prohibiting us from selling or licensing our drugs or technologies unless the holder licenses the patent or other proprietary rights to us, which it is not required to do; and • if a license is available from a holder, we may have to pay substantial royalties or grant cross- licenses to our patents or other proprietary rights. If any of these events occur, it could significantly harm our business and negatively affect our stock price. We may undertake infringement or other legal proceedings against third parties, causing us to spend substantial resources on litigation and exposing our own intellectual property portfolio to challenge. Third parties may infringe our patents. To prevent infringement or unauthorized use, we may need to file infringement suits, which are expensive and time- consuming. In an infringement proceeding, a court may decide that one or more of our patents is invalid, unenforceable, or both. In such case third parties may be able to use our technology without paying licensing fees or royalties. Even if the validity of our patents is upheld, a court may refuse to stop the other party from using the technology at issue on the ground that the other party' s activities are not covered by our patents. Policing unauthorized use of our intellectual property is difficult, and we may not be able to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States. In addition, third parties may affirmatively challenge our rights to, or the scope or validity of, our patent rights. The uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to conduct clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our drug candidates or other product candidates that we may identify to market. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. We may become involved in disputes with our strategic partners over intellectual property ownership, and publications by our research collaborators and clinical investigators could impair our ability to obtain patent protection or protect our proprietary information, either of which would have a significant impact on our business. Inventions discovered under our current or future strategic alliance agreements may become jointly owned by our strategic partners and us in some cases, and the exclusive property of one of us in other cases. Under some circumstances, it may be difficult to determine who owns a particular invention or whether it is jointly owned, and disputes could arise regarding ownership or use of those inventions. These disputes could be costly and time- consuming, and an unfavorable outcome could have a significant adverse effect on our business if we were not able to protect or license rights to these inventions. In addition, our research collaborators and clinical investigators generally have contractual rights to publish data arising from their work. Publications by our research collaborators and clinical investigators relating to our research and development programs, either with or without our consent, could benefit our current or potential competitors and may impair our ability to obtain patent protection or protect our proprietary information, which could significantly harm our business. We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that we or our employees have wrongfully used or disclosed trade secrets of their former employers. Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no legal proceedings against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail in defending these claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could hamper or prevent our ability to develop and commercialize certain

potential drugs, which could significantly harm our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and distract management. Financial Risks We have a history of significant losses and may not achieve or sustain profitability and, as a result, you may lose part or all of your investment. We have generally incurred operating losses in each year since our inception in 1997, due to costs incurred in connection with our research and development activities and general and administrative costs associated with our operations. Our drug candidates are all in early through late-stage clinical testing, and we must conduct significant additional clinical trials before we and our partners can seek the regulatory approvals necessary to begin commercial sales of our drugs. We expect to incur increasing losses for at least several more years, as we continue our research activities and conduct development of, and seek regulatory approvals for, our drug candidates, and commercialize any approved drugs. If our drug candidates fail or do not gain regulatory approval, or if our drugs do not achieve market acceptance, we will not be profitable. If we fail to become and remain profitable, or if we are unable to fund our continuing losses, you could lose part or all of your investment. We will need substantial additional capital in the future to sufficiently fund **and maintain** our operations. We have consumed substantial amounts of capital to date, and our operating expenditures will increase over the next several years as we expand our research and development activities and expand our organization to prepare for commercialization of any approved drug. We have funded our operations and capital expenditures with proceeds primarily from private and public sales of our equity securities, royalty monetization agreements, revenue interest agreements, strategic alliances, long- term debt, other financings, interest on investments and grants. We believe that our existing cash and cash equivalents, short- term investments and interest earned on investments should be sufficient to meet our projected operating requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development of our drug candidates and other research and development activities, including risks and uncertainties that could impact the rate of progress of our development activities, we are unable to estimate with certainty the amounts of capital outlays and operating expenditures associated with these activities. For the foreseeable future, our operations will require significant additional funding, in large part due to our research and development expenses, the organizational scale up and associated expenditures with commercial readiness activities to launch approved drugs combined with the absence of any revenues from product sales. Until we can generate a sufficient amount of product revenue, we expect to raise future capital through strategic alliance and licensing arrangements, public or private equity offerings and debt financings. We do not currently have any commitments for future funding other than through loans under the RP Loan Agreement with RPDF ~~, potential additional revenue interest sale proceeds under the RP Aficamten RPA,~~ and reimbursements, milestone and royalty payments that we may receive under our agreements with Ji Xing. We may not receive any further funds under any of these agreements. Our ability to raise funds may be adversely impacted by ~~current~~ **worsening** economic conditions **and the recent disruptions to, and volatility in, the credit and financial markets in the U. S. and worldwide resulting from the effects of inflationary pressures, potential future bank failures, global geopolitical factors including war or other hostilities, or otherwise** . As a result of these and other factors, we do not know whether additional financing will be available when needed, or that, if available, such financing would be on terms favorable to our stockholders or us, and if we cannot raise the funds we need to operate our business, we will need to delay or discontinue certain research and development activities, and our stock price may be negatively affected. We have never generated, and may never generate, revenues from commercial sales of our drugs and we may not have drugs to ~~market~~ **commercialize** for at least several years, if ever. We currently have no drugs for sale and we cannot guarantee that we will ever develop or obtain approval to market any drugs. To receive marketing approval for any drug candidate, we must demonstrate that the drug candidate satisfies rigorous standards of safety and efficacy to the FDA in the United States and other regulatory authorities abroad. We and our partners will need to conduct significant research and preclinical and clinical testing before we or our partners can file applications with the FDA or other regulatory authorities for approval of any of our drug candidates. In addition, to compete effectively, our drugs must be easy to use, cost-effective, covered by insurance or government sponsored medical plans, and economical to manufacture on a commercial scale, compared to other therapies available for the treatment of the same conditions. We may not achieve any of these objectives. Currently, our **late** clinical- stage drug candidates include omecamtiv mecarbil for the potential treatment of heart failure ~~, reldesemtiv for the potential treatment of ALS and potentially other indications associated with muscle weakness~~ , and aficamten for the potential treatment of HCM and potentially other indications. We cannot be certain that the clinical development of our current or any future drug candidates will be successful, that they will receive the regulatory approvals required to commercialize them, that they will ultimately be accepted by prescribers or reimbursed by insurers or that any of our other research programs will yield a drug candidate suitable for clinical testing or commercialization. For example, our NDA for omecamtiv mecarbil for the treatment of HFrEF resulted in a CRL notwithstanding the fact that GALACTIC- HF met its primary efficacy endpoint, and that the results from an additional clinical trial of omecamtiv mecarbil are required to establish substantial evidence of effectiveness for the treatment of HFrEF, with benefits that outweigh the risks. Our commercial revenues, if any, will be derived from sales of drugs that may not be commercially marketed for several years, if at all. The development of any one or all of these drug candidates may be discontinued at any stage of our clinical trials programs and we may not generate revenue from any of these drug candidates. Our indebtedness and liabilities could limit the cash flow available for our operations, expose us to risks that could adversely affect our business, financial condition and results of operations and impair our ability to satisfy our obligations under the 2026 Notes, the 2027 Notes and the RP Loan Agreement. As of December 31, ~~2022~~ **2023** , we had $ ~~611~~ **617** . ~~1~~ **5** million ~~aggregate principal amount~~ of ~~indebtedness,~~ **debt recorded on the balance sheet** comprised of ~~$ 50. 0 million under~~ the RP Loan Agreement **and the** ~~, $ 21. 1 million under our~~ 2026 ~~Notes,~~ and ~~$ 540. 0 million under our~~ 2027 **Convertible** Notes. We may also incur additional indebtedness to meet future financing needs. Our indebtedness could have significant negative consequences for our security holders and our business, results of operations and financial condition by, among other things: • increasing our vulnerability to adverse economic and industry conditions; •

limiting our ability to obtain additional financing; • requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, which will reduce the amount of cash available for other purposes; • limiting our flexibility to plan for, or react to, changes in our business; • diluting the interests of our existing stockholders as a result of issuing shares of our common stock upon conversion of the Convertible Notes; and • placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital. Our business may not generate sufficient funds, and we may otherwise be unable to maintain sufficient cash reserves, to pay amounts due under our indebtedness and our cash needs may increase in the future. In addition, any required repurchase of the Convertible Notes for cash as a result of a fundamental change would lower our current cash on hand such that we would not have those funds available for us in our business. Further any future indebtedness that we may incur may contain financial and other restrictive covenants that limit our ability to operate our business, raise capital or make payments under our other indebtedness. If we fail to comply with these covenants or to make payments under our indebtedness when due, then we would be in default under that indebtedness, which could, in turn, result in that and our other indebtedness becoming immediately payable in full. Covenants in the RP Loan Agreement, the RP Aficamten RPA, the RP OM RPA, and the indentures related to our Convertible Notes restrict our business and operations in many ways and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected. Our operations may not provide sufficient cash to meet our debt repayment obligations. The RP Loan Agreement, the RP Aficamten RPA, the RP OM RPA, and the indentures related to the Convertible Notes require that we comply with certain covenants applicable to us, including among other things, covenants restricting dispositions, changes in business, management, ownership or business locations, mergers or acquisitions, indebtedness, encumbrances, distributions, investments, transactions with affiliates and subordinated debt, any of which could restrict our business and operations, particularly our ability to respond to changes in our business or to take specified actions to take advantage of certain business opportunities that may be presented to us. In addition, the RP Aficamten RPA and the RP OM RPA contain certain covenants applicable to us, including among other things, development and commercialization diligence obligations in connection to aficamten and omecamtiv mecarbil and reporting obligations, which could also restrict our business and operations, particularly in connection to our development and commercialization of aficamten and omecamtiv mecarbil. Our failure to comply with any of the covenants could result in a default under the RP Loan Agreement, the RP Aficamten RPA, the RP OM RPA, or the indentures related to the Convertible Notes, which could permit the counterparties to declare all or part of any outstanding borrowings or other payment obligations to be immediately due and payable and / or enforce any outstanding liens against our assets. We have no rights to repurchase the revenue interests in omecamtiv mecarbil or aficamten sold to RPFT or RPI ICAV respectively, thereby limiting our ability to eliminate future applicability of the covenants contained in the RP OM RPA and the RP Aficamten RPA, and although we do have voluntary prepayment rights under the RP Loan Agreement, any voluntary prepayment rights will require that we pay RPDF 190 % of the principal amount of amounts disbursed to us as tranche 1, tranche 4 and tranche 5 loans and 200 % for tranche 2 and tranche 3 loans, thereby making it potentially disadvantageous to voluntarily prepay RPDF prior to the final maturity date applicable to loans outstanding under the RP Loan Agreement. In addition, certain provisions in the 2026 Notes, the 2027 Notes and the related indentures could make a third- party attempt to acquire us more difficult or expensive. For example, if a takeover constitutes a fundamental change under our indenture, then noteholders will have the right to require us to repurchase their notes for cash. In addition, if a takeover constitutes a make-whole fundamental change under our indenture, then we may be required to temporarily increase the conversion rate. In either case, and in other cases, our obligations under the Convertible Notes and the related Indentures could increase the cost of acquiring us or otherwise discourage a third party from acquiring us or removing incumbent management, including in a transaction that noteholders or holders of our common stock may view as favorable. Finally, should we be unable to comply with our covenants or if we default on any portion of our outstanding borrowings under the RP Loan Agreement, in addition to its rights to accelerate and demand for immediate repayment of amounts outstanding under the RP Loan Agreement, we would be liable for default interest at a rate of 4 % over the prime rate. We may not be entitled to obtain additional loan disbursements under the RP Loan Agreement ~~or the RP Aficamten RPA~~. On January 7, 2022, we announced that we had entered into the RP Loan Agreement ~~and the RP Aficamten RPA~~ with ~~each of~~ RPDF ~~and RPI ICAV respectively~~, ~~each~~ such entity being affiliated with Royalty Pharma International plc. ~~Together these~~ **The RP Loan** ~~agreements~~ **Agreement** ~~make~~ **makes** available to us ~~up to $ 150. 0 million in revenue interest sale proceeds under the RP Aficamten RPA and~~ up to $ 300. 0 million in loans, of which a $ 50. 0 million loan **was** ~~and $ 50. 0 million in revenue interest sale proceeds were~~ paid to us at the closing of such ~~transactions~~ **transaction**. ~~In~~ **With the positive results of SEQUOIA- HCM, we have satisfied the conditions related to tranche 4 of the RP Loan Agreement and thus an** ~~addition~~ **additional** ~~, on~~ **$ 75 million in loans are currently available to us for disbursement. Tranche 5 of the RP Loan Agreement would be available to us upon acceptance for filing by FDA of an NDA for aficamten. Should we not satisfy such condition for tranche 5 by** March ~~10~~ **31**, ~~2022~~ **2025**, **or** ~~we received a further $ 50. 0 million~~ in ~~revenue interest sale proceeds from RPI ICAV~~ **the event we fail to meet our obligations or default** under the **agreement** ~~RP Aficamten RPA following the initiation of our first pivotal trial in oHCM for aficamten. However~~, **the actual amount of** additional loan disbursements ~~and sale proceeds under the RP Aficamten RPA and the RP Loan Agreement are subject to our satisfaction of certain conditions related to the development of aficamten and omecamtiv mecarbil, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or in the event we fail to meet our obligations or default under these agreements, the actual amount of additional loan disbursements and / or sale proceeds~~ could be substantially less than the maximum amounts available thereunder. ~~As~~ **For example, as** a result of FDA' s CRL in response to our NDA for omecamtiv mecarbil, we ~~do~~ **have** not ~~expect to satisfy~~ **satisfied** the conditions for the availability of disbursement of the $ 50 million tranche 2 and $ 25 million tranche 3 term loans under the RP Loan Agreement. We are subject to counterparty risk under the RP ~~Aficamten RPA and the RP~~ Loan Agreement We are subject to counterparty risk in the event that ~~either~~ RPDF ~~or RP ICAV default~~ **defaults** on **its** ~~their respective~~ obligations under the RP Loan Agreement ~~or the RP~~

~~Aficamten RPA respectively. In respect of the RP-Aficamten RPA, our ability to receive additional revenue interest sale proceeds is subject to the risk that RPI ICAV may default or otherwise fail to perform its obligations thereunder to pay us additional revenue interest sale proceeds that we would be entitled to upon satisfaction of certain conditions. In such event, subject to a cure right of RPI ICAV, we will have a limited right to reduce the amount of royalty payable by unless such obligation is contested in good faith, but otherwise our exposure to the credit risk of RPI ICAV will not be secured by any collateral. If RPI ICAV becomes subject to insolvency proceedings, we will become an unsecured creditor in those proceedings with a claim equal to our exposure at the time under such transaction and without any reversion of the revenue interest having been sold to RPI ICAV (other than the aforementioned reduction) and without any recourse against Royalty Pharma International plc or any of its other affiliated or controlled entities. In respect of the RP-Loan Agreement, our ability to receive additional loan disbursements is subject to the risk that RPDF may default or otherwise fail to perform its obligations thereunder to extend additional loan disbursement that we would be entitled to upon satisfaction of certain conditions~~ . In such event, we have no recourse against Royalty Pharma International plc or any of its other affiliated or controlled entities, and in the event of an RPDF insolvency, we would have no rights to additional loan disbursements from RPDF. Conversion of our outstanding Convertible Notes may result in the dilution of existing stockholders, create downward pressure on the price of our common stock, and restrict our ability to take advantage of future opportunities. The Convertible Notes may be converted into cash and shares of our common stock (subject to our right or obligation to pay cash in lieu of all or a portion of such shares). If shares of our common stock are issued to the holders of the Convertible Notes upon conversion, there will be dilution to our stockholders' equity and the market price of our shares may decrease due to the additional selling pressure in the market. Any downward pressure on the price of our common stock caused by the sale or potential sale of shares issuable upon conversion of the Convertible Notes could also encourage short sales by third parties, creating additional selling pressure on our stock. The existence of the Convertible Notes and the obligations that we incurred by issuing them may restrict our ability to take advantage of certain future opportunities, such as engaging in future debt or equity financing activities. We will depend on Ji Xing for the development and commercialization of aficamten and omecamtiv mecarbil in China and Taiwan. Under the terms of the Ji Xing Agreements, Ji Xing will be responsible for the development and commercialization of aficamten and omecamtiv mecarbil in China and Taiwan. The timing and amount of any milestone and royalty payments we may receive under the Ji Xing Agreements will depend in part on the efforts and successful commercialization of aficamten and omecamtiv mecarbil by Ji Xing. We do not control the individual efforts of Ji Xing, and any failure by Ji Xing to devote sufficient time and effort to the development and commercialization of aficamten or omecamtiv mecarbil or to meet its obligations to us, including for future milestone and royalty payments; or to adequately deploy business continuity plans in the event of a crisis, or to satisfactorily resolve significant disagreements with us could each have an adverse impact on our financial results and operations. We will also depend on Ji Xing to comply with all applicable laws relative to the development and commercialization of aficamten and omecamtiv mecarbil in China and Taiwan. If Ji Xing were to violate, or was alleged to have violated, any laws or regulations during the performance of its obligations for us, it is possible that we could suffer financial and reputational harm or other negative outcomes, including possible legal consequences. Any termination, breach or expiration of the Ji Xing Agreements could have a material adverse effect on our financial position by reducing or eliminating the potential for us to receive milestones and royalties. In such an event, we may be required to devote additional efforts and to incur additional costs associated with pursuing the development and commercialization of aficamten and omecamtiv mecarbil in China and Taiwan. Alternatively, we may attempt to identify and transact with a new sub- licensee, but there can be no assurance that we would be able to identify a suitable sub- licensee or transact on terms that are favorable to us. Our ability to use net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations, and ownership changes may limit our ability to use our net operating losses and tax credits in the future. Our ability to use our federal and state NOLs to offset potential future taxable income and reduce related income taxes depends upon our generation of future taxable income. We cannot predict with certainty when, or whether, we will generate sufficient taxable income to use our NOLs. Our federal NOLs generated in taxable years beginning prior to 2018 will continue to be governed by tax rules in effect prior to the Tax Act, with unused NOLs expiring 20 years after we report a tax loss. These NOLs could expire unused and be unavailable to offset future taxable income. We cannot predict if and to what extent various states will conform to the Tax Act, as modified by additional tax legislation enacted in 2020. In addition, generally, if one or more stockholders or groups of stockholders who owns at least 5 % of our stock increases its ownership by more than 50 % over its lowest ownership percentage within a three-year testing period, an ownership change occurs (an " Ownership Change "). Our ability to utilize our NOLs and tax credit carryforwards to reduce taxes payable in a year we have taxable income may be limited if there has been an Ownership Change in our stock. Similar rules may apply under state tax laws. We may experience Ownership Changes in the future as a result of future stock sales or other changes in the ownership of our stock, some of which are beyond our control and, as a result, NOLs generated in taxable years beginning 2017 and before, may expire unused. Any material limitation or expiration of our NOLs and tax credit carryforwards may harm our future net income by effectively increasing our future effective tax rate, which could result in a reduction in the market price of our common stock. Comprehensive U. S. tax reform legislation could increase the tax burden on our orphan drug programs and adversely affect our business and financial condition. In 2017, the U. S. government enacted the Tax Act that includes significant changes to the taxation of business entities, which was modified by additional federal tax legislation in 2020. ~~These~~ -- **The** ~~changes include, among others, (i) a permanent reduction to the corporate income tax rate, (ii) a partial limitation on the deductibility of business interest expense and net operating loss carryforwards, (iii) a shift of the U. S. taxation of multinational corporations from a tax on worldwide income to a territorial system (along with certain rules designed to prevent erosion of the U. S. income tax base) and (iv) a one- time tax on accumulated offshore earnings held in cash and illiquid assets, with the latter taxed at a lower rate. Further, the~~ comprehensive tax legislation, among other things, reduces the orphan drug tax credit from 50 % to 25 % of qualifying expenditures. When and if we become profitable, this

reduction in tax credits may result in an increased federal income tax burden on our orphan drug programs as it may cause us to pay federal income taxes earlier under the revised tax law than under the prior law and, despite being partially off- set by a reduction in the corporate tax rate from a top marginal rate of 35 % to a flat rate of 21 %, may increase our total federal tax liability attributable to such programs. Notwithstanding the reduction in the corporate income tax rate, the overall impact of this comprehensive tax legislation resulted in an overall reduction in our deferred tax assets, and our business and financial condition could still be adversely affected as additional guidance and regulations are issued with respect to the original tax law change. In addition, it is uncertain if and to what extent various states will conform to this comprehensive tax legislation, and states may enact suspensions or limitations on the use of net operating losses and tax credits. The impact of the 2017 tax legislation on holders of our common stock is also uncertain and could be adverse. ~~Investors should consult with their legal and tax advisors with respect to this comprehensive tax legislation and the potential tax consequences of investing in or holding our common stock.~~ We are obligated to ~~develop and~~ maintain proper and effective internal control over financial reporting. In the future, we may not complete our execution of our internal control over financial reporting in a timely manner, or these internal controls may not be determined to be effective, which may result in ~~additional~~ material misstatements in our consolidated financial statements and may adversely affect investor confidence in our company and, as a result, the value of our common stock. We are required, pursuant to Section 404 of the Sarbanes- Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting. Complying with Section 404 requires a rigorous compliance program as well as adequate time and resources. We may not be able to complete our internal control evaluation, testing and any required remediation in a timely fashion. Additionally, if we identify one or more material weaknesses in our internal control over financial reporting, we will not be able to assert that our internal controls are effective. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. If material weaknesses are identified in the future or we are not able to comply with the requirements of Section 404 in a timely manner, our reported financial results could be materially misstated, we would receive an adverse opinion regarding our internal controls over financial reporting from our independent registered public accounting firm, and we could be subject to investigations or sanctions by regulatory authorities, which would require additional financial and management resources, and the value of our common stock could decline. To the extent we identify future weaknesses or deficiencies, there could be material misstatements in our consolidated financial statements and we could fail to meet our financial reporting obligations. As a result, our ability to obtain additional financing, or obtain additional financing on favorable terms, could be materially and adversely affected which, in turn, could materially and adversely affect our business, our financial condition and the value of our common stock. If we are unable to assert that our internal control over financial reporting is effective in the future, or if our independent registered public accounting firm is unable to express an opinion or expresses an adverse opinion on the effectiveness of our internal controls in the future, investor confidence in the accuracy and completeness of our financial reports could be further eroded, which would have a material adverse effect on the price of our common stock. Our reported financial results may be adversely affected by changes in accounting principles generally accepted in the U. S. We prepare our financial statements in conformity with accounting principles generally accepted in the U. S. These accounting principles are subject to interpretation by the FASB and the SEC. A change in these policies or interpretations could have a significant effect on our reported financial results, may retroactively affect previously reported results, could cause unexpected financial reporting fluctuations, and may require us to make costly changes to our operational processes and accounting systems. Legal and Compliance Risks Recently enacted laws, including the Inflation Reduction Act, or IRA, and potential future legislation may increase the difficulty and cost for us to obtain regulatory approval of, and to commercialize our products and affect the prices we may obtain upon commercialization. The regulations that govern, among other things, regulatory approvals, coverage, pricing and reimbursement for new drug products vary widely from country to country. In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay regulatory approval of our product candidates, restrict or regulate post- approval activities and affect our ability to successfully sell any product candidates for which we obtain regulatory approval. In particular, in March 2010, the ACA was enacted, which substantially changed the way health care is financed by both governmental and private insurers, and continues to significantly impacts the U. S. pharmaceutical industry. The ACA and its implementing regulations, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our product candidates that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, provided incentives to programs that increase the federal government' s comparative effectiveness research and established a new Medicare Part D coverage gap discount program. Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by the U. S. Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $ 1. 2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation' s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2 % per fiscal year, which went into effect in April 2013, and, due to subsequent legislative amendments, will remain in effect until ~~2031~~ **2032** unless additional Congressional action is taken ~~. Under current legislation, the actual reduction in Medicare payments will vary from 1 % in 2022 to up to 4 % in the final fiscal year of this sequester~~. In January 2013, the American Taxpayer Relief Act of 2012 was enacted which, among other things, further reduced Medicare payments to several providers, including hospitals and outpatient clinics, and increased the statute of limitations period for the

government to recover overpayments to providers from three to five years. Since its enactment, there have been executive, judicial and Congressional challenges to numerous elements of the ACA, as well as efforts to repeal or replace certain aspects of the ACA. For example, on June 17, 2021, the U. S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the " individual mandate " was repealed by Congress. It is possible that the ACA will be subject to executive, judicial, and Congressional challenges in the future. It is unclear how any such challenges will impact the ACA and our business. Policy changes, including potential modification or repeal of all or parts of the ACA or the implementation of new health care legislation, could result in significant changes to the health care system which may adversely affect our business in unpredictable ways. In August 2022, the Inflation Reduction Act, or IRA, was signed into law, which, among other things, includes prescription drug provisions that may impact product pricing including the potential for net price reductions and / or the ability to increase price beyond the level of inflation over the lifecycle of our products, and / or may increase our rebate obligation to Medicare. Provisions include a requirement that the HHS negotiate drug prices for single- source brand- name drugs and biologics that are among the 50 drugs with the highest total Medicare Part D spending. The law establishes a maximum fair price, outlines the process by which the Secretary of HHS will identify drugs for negotiations, and establishes non- compliance penalties for manufacturers. The IRA implements inflation rebates in Medicare when a drug' s Average Manufacturer Price (AMP, in Part D) or Average Sale Price (ASP, in Part B) rises faster than the inflation index (CPI-U). In addition, the Part D drug benefit caps beneficiary spending at $ 2, 000, eliminates the coverage gap for patients, and modifies, beginning in 2025, liabilities for drug manufacturers by replacing the 70 % discount in the Coverage gap with a 10 % discount in the Initial Coverage phase and a 20 % discount in the Catastrophic phase. **The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges.** There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. However, we cannot predict the timing or substance of proposals that may be adopted in the future, particularly in light of the difficulty of advancing legislation through Congress. The continuing efforts of governments, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare, including by imposing price controls, may adversely affect the demand and / or potential sales for our product candidates for which we obtain regulatory approval and our ability to set a price that we believe is fair for our products. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Legislative and regulatory proposals have been made to expand post- approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of these changes on the regulatory approvals of our product candidates, if any, may be. In the United States, the E. U. and other potentially significant markets for our product candidates, government authorities and third- party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which has resulted in lower average selling prices. For example, in the United States, there have been several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. **For example, on January 5, 2024, the FDA approved Florida' s Section 804 Importation Program (SIP) proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs** In addition to the enactment of the IRA, **in response to** the Biden administration ~~released an additional~~ **' s October 2022** executive order **,** on ~~October~~ **February** 14, ~~2022~~ **2023** , ~~directing~~ HHS ~~to~~ **released a** report **outlining** ~~on how the~~ **three** ~~Center for Medicare and Medicaid Innovation can be further leveraged to test~~ new models for ~~lowering drug costs~~ **testing by the Centers** for Medicare ~~and~~ **&** Medicaid ~~beneficiaries~~ **Services Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs through the use of march- in rights under the Bayh- Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March- In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march- in rights. While march- in rights have not previously been exercised, it is uncertain if that will continue under the new framework** . Furthermore, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the E. U. will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. We cannot predict the likelihood, nature, or extent of health reform initiatives that may arise from future legislation or administrative action. Our relationships with customers, healthcare providers, clinical trial sites and professionals and third-

party payors will be subject to applicable anti- kickback, fraud and abuse and other laws and regulations. If we fail to comply with federal, state and foreign laws and regulations, including healthcare, privacy and data security laws and regulations, we could face criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Healthcare providers, including physicians and third- party payors play a primary role in the recommendation and prescription of any drug candidates for which we may obtain marketing approval. Our arrangements with customers, healthcare providers and third- party payors may expose us 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 develop, and may market, sell and distribute, our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include, but are not limited to, the following: • The federal healthcare anti- kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward 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 federally funded healthcare programs such as Medicare and Medicaid. This statute has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others. Several other countries, including the United Kingdom, have enacted similar anti- kickback, fraud and abuse, and healthcare laws and regulations. • The federal false claims laws, including the False Claims Act, which can be enforced through whistleblower or qui tam actions, imposes penalties against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. The government and qui tam relators have brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be submitted to the government. • HIPAA imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program. HIPAA also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. HIPAA also imposes criminal liability for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services **. • In addition, HIPAA, as amended by Health Information Technology for Economic and Clinical Health Act of 2009 (“ HITECH ”), imposes certain requirements on covered entities, which include certain healthcare providers, health plans and healthcare clearinghouses, and their business associates and covered subcontractors that receive or obtain protected health information in connection with providing a service on behalf of a covered entity relating to the privacy, security and transmission of individually identifiable health information** . • The federal Physician Payments Sunshine Act requires manufacturers of drugs, devices, biologics and medical supplies to report to the HHS information related to payments and other transfers of value made to or at the request of physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other health care professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members. Payments made to physicians and research institutions for clinical trials are included within the ambit of this law. • Analogous state laws and regulations, such as state anti- kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry’ s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures and state and local laws that require the registration of sales representatives. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Exclusion, suspension and debarment from government funded healthcare programs would significantly impact our ability to commercialize, sell or distribute any drug. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. We may be subject to costly product liability or other liability claims and may not be able to obtain adequate insurance. The use of our drug candidates in clinical trials may result in adverse events. We cannot predict all the possible harms or adverse events that may result from our clinical trials. We currently maintain limited product liability insurance. We may not have sufficient resources to pay for any liabilities resulting from a personal injury or other claim excluded from, or beyond the limit of, our insurance coverage. Our insurance does not cover third parties’ negligence or malpractice, and our clinical investigators and sites may have inadequate insurance or none at all. In addition, in order to conduct clinical trials or otherwise carry out our business, we may have to contractually assume liabilities for which we may not be insured. If we are unable to look to our own insurance or a third party’ s insurance to pay claims against us, we may have to pay any arising costs and damages ourselves, which may be substantial. In addition, if we commercially launch drugs based on our drug candidates, we will face even greater exposure to product liability claims. This risk exists even with respect to those drugs that are approved for commercial sale by the FDA and foreign regulatory agencies and manufactured in licensed and regulated facilities. We intend to secure additional limited product liability insurance coverage for drugs that we commercialize, but may not be able to obtain such insurance on acceptable terms with adequate coverage, or at reasonable costs. Even if we are ultimately successful in product liability litigation, the litigation would consume substantial amounts of our financial and managerial resources and may

create adverse publicity, all of which would impair our ability to generate sales of the affected product and our other potential drugs. Moreover, product recalls may be issued at our discretion or at the direction of the FDA and foreign regulatory agencies, other governmental agencies or companies having regulatory control for drug sales. Product recalls are generally expensive and often have an adverse effect on the reputation of the drugs being recalled and of the drug' s developer or manufacturer. We may be required to indemnify third parties against damages and other liabilities arising out of our development, commercialization and other business activities, which could be costly and time- consuming and distract management. If third parties that have agreed to indemnify us against damages and other liabilities arising from their activities do not fulfill their obligations, then we may be held responsible for those damages and other liabilities. European data collection is governed by restrictive regulations governing the collection, use, processing and cross- border transfer of personal information. We may collect, process, use or transfer personal information from individuals located in the E. U. in connection with our business, including in connection with conducting clinical trials in the E. U. Additionally, if any of our product candidates are approved, we may seek to commercialize those products in the E. U. The collection and use of personal health data in the E. U. are governed by the provisions of the GDPR. This legislation imposes requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside of the EEA, including to the U. S., providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments and record- keeping. The GDPR imposes additional responsibilities and liabilities in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. Failure to comply with the requirements of the GDPR and related national data protection laws of the member states of the E. U. may result in substantial fines, other administrative penalties and civil claims being brought against us, which could have a material adverse effect on our business, financial condition and results of operations. European data protection laws, including the GDPR, generally restrict the transfer of personal information from Europe, including the EEA, United Kingdom and Switzerland, to the United States and most other countries unless the parties to the transfer have implemented specific safeguards to protect the transferred personal information. One of the primary safeguards allowing United States companies to import personal information from Europe has been certification to the EU- U. S. Privacy Shield and Swiss- U. S. Privacy Shield frameworks administered by the United States Department of Commerce. However, the Court of Justice of the EU recently invalidated the EU- U. S. Privacy Shield. The same decision also raised questions about whether one of the primary alternatives to the EU- U. S. Privacy Shield, namely, the European Commission' s Standard Contractual Clauses, can lawfully be used for personal information transfers from Europe to the United States or most other countries. At present, there are few, if any, viable alternatives to the EU- U. S. Privacy Shield and the Standard Contractual Clauses. Although we rely primarily on individuals' explicit consent to transfer their personal information from Europe to the United States and other countries, in certain cases we have relied or may rely on the Standard Contractual Clauses. Authorities in the United Kingdom and Switzerland, whose data protection laws are similar to those of the EU, may similarly invalidate use of the EU- U. S. Privacy Shield and Swiss- U. S. Privacy Shield, respectively, as mechanisms for lawful personal information transfers from those countries to the United States. As such, if we are unable to rely on explicit consent to transfer individuals' personal information from Europe, which can be revoked, or implement another valid compliance solution, we will face increased exposure to substantial fines under European data protection laws as well as injunctions against processing personal information from Europe. Inability to import personal information from the EEA, United Kingdom or Switzerland may also restrict our clinical trial activities in Europe; limit our ability to collaborate with CROs, service providers, contractors and other companies subject to European data protection laws; and require us to increase our data processing capabilities in Europe at significant expense. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross- border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of delivering our services and operating our business. Responding to any claims relating to improper handling, storage or disposal of the hazardous chemicals and radioactive and biological materials we use in our business could be time- consuming and costly. Our research and development processes involve the controlled use of hazardous materials, including chemicals and radioactive and biological materials. Our operations produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from those materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may be sued for any injury or contamination that results from our or third parties' use of these materials. Compliance with environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production activities. General Risk Factors Our failure to attract and retain skilled personnel could impair our drug development, commercialization and financial reporting activities. Our business depends on the performance of our senior management and key scientific, commercial and technical personnel. The loss of the services of any member of our senior management or key scientific, technical, commercial or financial reporting staff may significantly delay or prevent the achievement of drug development and other business objectives by diverting management' s attention to transition matters and identifying suitable replacements. We also rely on consultants and advisors to assist us in formulating our research and development strategy. All of our consultants and advisors are either self- employed or employed by other organizations, and they may have conflicts of interest or other commitments, such as consulting or advisory contracts with other organizations, that may affect their ability to contribute to us. In addition, if and as our business grows, we will need to recruit additional executive management and scientific, technical and financial reporting personnel. There is intense competition for skilled executives and employees with relevant scientific and technical expertise, and this competition is likely to continue. Our inability to attract and retain sufficient scientific, technical, commercial

and managerial personnel could limit or delay our product development or commercialization activities, which would adversely affect the development of our drug candidates and commercialization of our potential drugs and growth of our business. Our internal computer systems, or those of our CROs, CMOs, supply chain partners, collaboration partners or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our drug development programs. Despite the implementation of security measures, our internal computer systems and those of our third- party CROs, CMOs, supply chain partners, collaboration partners and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical study data from completed or ongoing clinical studies for any of our drug candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our operations could be compromised and the further development of our product candidates could be delayed. Significant disruptions of information technology systems or breaches of data security could adversely affect our business. Our business is increasingly dependent on complex and interdependent information technology systems, including internet- based systems, databases and programs, to support our business processes as well as internal and external communications. As use of information technology systems has increased, deliberate attacks and attempts to gain unauthorized access to computer systems and networks have increased in frequency and sophistication. Our information technology, systems and networks are potentially vulnerable to breakdown, malicious intrusion and computer viruses which may result in the impairment of production and key business processes or loss of data or information. We are also potentially vulnerable to data security breaches — whether by employees or others — which may expose sensitive data to unauthorized persons. We have in the past and may in the future be subject to security breaches. For example, in February 2018, we discovered that our e- mail server suffered unauthorized intrusions in which proprietary business information was accessed. In addition, in December 2019, one of our employee' s email account suffered an unauthorized intrusion, leading to the submission and inadvertent payment of a fraudulent invoice in the amount of approximately one hundred thousand dollars. In December 2019, our IT systems were exposed to a ransomware attack, which partially impaired certain IT systems for a short period of time. ~~Finally, in September 2020, one of our employees' email account suffered unauthorized access as result of a phishing incident, but we believe no sensitive information was accessed.~~ Although we do not believe that we have experienced any material losses related to security breaches, including in three recent email " phishing " incidents or the ransomware attack, there can be no assurance that we will not suffer such losses in the future. Breaches and other inappropriate access can be difficult to detect and any delay in identifying them could increase their harm. While we have implemented measures to protect our data security and information technology systems, such measures may not prevent these events. Any such breaches of security and inappropriate access could disrupt our operations, harm our reputation or otherwise have a material adverse effect on our business, financial condition and results of operations. Our facilities in California are located near an earthquake fault, and an earthquake or other types of natural disasters, catastrophic events or resource shortages could disrupt our operations and adversely affect our results. All our facilities and our important documents and records, such as hard and electronic copies of our laboratory books and records for our drug candidates and compounds and our electronic business records, are located in our corporate headquarters at a single location in South San Francisco, California near active earthquake zones. If a natural disaster, such as an earthquake, fire or flood, a catastrophic event such as a disease pandemic or terrorist attack, or a localized extended outage of critical utilities or transportation systems occurs, we could experience a significant business interruption. Our partners and other third parties on which we rely may also be subject to business interruptions from such events. In addition, California from time to time has experienced shortages of water, electric power and natural gas. Future shortages and conservation measures could disrupt our operations and cause expense, thus adversely affecting our business and financial results. We expect that our stock price will fluctuate significantly, and you may not be able to resell your shares at or above your investment price. The stock market, particularly in recent years, has experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks, which often does not relate to the operating performance of the companies represented by the stock. **For example, in 2023, the closing price of our common stock on the Nasdaq Global Select Market ranged from $ 25. 98 to $ 87. 58.** Factors that **have caused and** could cause **in the future** volatility in the market price of our common stock include, but are not limited to: • announcements concerning any of the clinical trials for our drug candidates (including, but not limited to, the timing of initiation or completion of such trials and the results of such trials, and delays or discontinuations of such trials, including delays resulting from slower than expected or suspended patient enrollment or discontinuations resulting from a failure to meet pre- defined clinical end points); • announcements concerning our strategic alliances; • failure or delays in entering additional drug candidates into clinical trials; • failure or discontinuation of any of our research programs; • issuance of new or changed securities analysts' reports or recommendations; • failure or delay in establishing new strategic alliances, or the terms of those alliances; • market conditions in the pharmaceutical, biotechnology and other healthcare- related sectors; • actual or anticipated fluctuations in our quarterly financial and operating results; • developments or disputes concerning our intellectual property or other proprietary rights; • introduction of technological innovations or new products by us or our competitors; • issues in manufacturing, packaging, labeling and distribution of our drug candidates or drugs; • market acceptance of our drugs; • third- party healthcare coverage and reimbursement policies; • FDA or other U. S. or foreign regulatory actions affecting us or our industry; • litigation or public concern about the safety of our drug candidates or drugs; • additions or departures of key personnel; • substantial sales of our common stock by our existing stockholders, whether or not related to our performance; • automated trading activity by algorithmic and high- frequency trading programs; • volatility in the stock prices of other companies in our industry or in the stock market generally; and • other factors described in this " Risk Factors " section. These and other external factors **have**

caused and may cause the market price and demand for our common stock to fluctuate substantially, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. In addition, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert our management' s time and attention. If securities or industry analysts publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline. The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline. ~~In addition, as required by the revenue recognition standard, ASC 606, Revenue from Contracts with Customers, Revenue from Contracts with Customers, we disclose the aggregate unsatisfied amount of transaction price allocated to performance obligations as of the end of the reporting period. It is possible that analysts and investors could misinterpret our disclosure or that the terms of our research or license agreements or other circumstances could cause our methods for preparing this disclosure to differ significantly from others, which could lead to inaccurate or unfavorable forecasts by analysts and investors.~~ Regardless of accuracy, unfavorable interpretations of our financial information and other public disclosures could have a negative impact on our stock price. If our financial performance fails to meet analyst estimates, for any of the reasons discussed above or otherwise, or one or more of the analysts who cover us downgrade our common stock or change their opinion of our common stock, our stock price would likely decline. We have never paid dividends on our capital stock, and we do not anticipate paying any cash dividends in the foreseeable future. We have paid no cash dividends on any of our classes of capital stock to date and we currently intend to retain our future earnings, if any, to fund the development and growth of our businesses. In addition, the terms of existing or any future debts may preclude us from paying these dividends ~~. A rating agency may not rate the notes or may assign a rating that is lower than expected. We do not intend to seek to have the 2027 Notes rated by any rating agency. However, if one or more rating agencies rates the notes and assigns a rating that is lower than the rating that investors expect, or reduces their rating in the future, then the trading price of our common stock and the 2027 Notes could significantly decline. In addition, market perceptions of our creditworthiness will directly affect the trading price of our common stock and the 2027 Notes. Accordingly, if a ratings agency rates any of our indebtedness in the future or downgrades or withdraws the rating, or puts us on credit watch, then the trading price of our common stock and the 2027 Notes will likely decline~~ . Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management. Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions: • establish a classified board of directors with three- year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors; • eliminate cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates; • establish the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors; • prohibit removal of directors without cause; • authorize our board of directors to issue preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquirer; • authorize our board of directors to alter our bylaws without obtaining stockholder approval; • require the approval of at least two- thirds of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors; • prohibit stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders; • require that a special meeting of stockholders be called only by the chairman of the board of directors, the chief executive officer, the president or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and • provide for advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer' s own slate of directors or otherwise attempting to obtain control of us. We are also subject to the anti- takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15 % or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock. Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful third- party claims against us and may reduce the amount of money available to us. Our amended and restated certificate of incorporation and amended and restated bylaws provide that we will indemnify our directors and officers, in each case to the fullest extent permitted by

Delaware law. In addition, as permitted by Section 145 of the Delaware General Corporation Law, our amended and restated bylaws and our indemnification agreements that we have entered into with our directors and officers provide that: • we will indemnify our directors and officers for serving us in those capacities or for serving other business enterprises at our request, to the fullest extent permitted by Delaware law. Delaware law provides that a corporation may indemnify such person if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the registrant and, with respect to any criminal proceeding, had no reasonable cause to believe such person' s conduct was unlawful; • we may, in our discretion, indemnify employees and agents in those circumstances where indemnification is permitted by applicable law; • we are required to advance expenses, as incurred, to our directors and officers in connection with defending a proceeding, except that such directors or officers shall undertake to repay such advances if it is ultimately determined that such person is not entitled to indemnification; • we will not be obligated pursuant to our amended and restated bylaws to indemnify a person with respect to proceedings initiated by that person against us or our other indemnitees, except with respect to proceedings authorized by our board of directors or brought to enforce a right to indemnification; • the rights conferred in our amended and restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons; and • we may not retroactively amend our amended and restated bylaw provisions to reduce our indemnification obligations to directors, officers, employees and agents.