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

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An investment in our securities involves a high degree of risk. You should carefully consider the risks summarized in Item 1A, " **“** Risk Factors, " **”** included in this report. These risks include, but are not limited to, the following: • We have a limited operating history, have incurred significant operating losses since our inception and expect to incur significant losses for the foreseeable future. We may never generate any revenue or become profitable or, if we achieve profitability, we may not be able to sustain it. • We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could ~~force~~ **lead** us to delay, limit, reduce **, abandon** or terminate our product development programs, commercialization efforts or other operations. • Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates. • We are early in our development efforts and have **two** ~~only three~~ product candidates in clinical development. All of our other research programs are still in the preclinical or discovery stage. If we are unable to successfully develop **any** product candidates or experience significant delays in doing so, our business will be materially harmed. • We cannot assure you that we will be able to successfully **discover and** develop any product candidates. • Preclinical and clinical drug development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies and early clinical trials are not necessarily predictive of future results. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval. • Any delays in the commencement or completion, or **any** termination or suspension, of our clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects. • ~~The COVID- 19 pandemic, related variants and other epidemic diseases could adversely impact our business, including our drug manufacturing, nonclinical activities and clinical trials. •~~ We may find it difficult to enroll **and retain** patients in our clinical trials given the limited number of patients who have the diseases for which our product candidates are being developed **, which could delay** ~~. • If we encounter difficulties enrolling subjects in our~~ **or** ~~clinical trials,~~ **otherwise adversely affect** our clinical development activities **. • Use of our product candidates** could be ~~delayed~~ **associated with side effects** or ~~otherwise adversely~~ -- **adverse** ~~affected~~ **events, which could severely harm our business, reputation, prospects, operating results and financial condition** . • Our product candidates are subject to extensive regulation and compliance, which is costly and time consuming and which may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates **. • We have conducted, and continue to conduct, clinical trials for our current product candidates outside of the United States, and we may do so for our other product candidates. However, conducting trials outside of the United States exposes us to additional risks, which could materially harm our business. • Initial, interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data becomes available and is subject to audit and verification procedures that could result in material changes in the final data. • We rely on third parties for raw materials, active pharmaceutical ingredients, and drug product intermediates for the manufacture of our product candidates for preclinical and clinical development and expect to continue to do so for the foreseeable future. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts** . • We face competition from entities that have developed or may develop somatostatin agonist products or other ~~product~~ **competitive** candidates. If these companies develop **competing** technologies or product candidates more rapidly than we do or their technologies are more effective, our ability to develop and successfully commercialize products may be adversely affected. • ~~We rely on third parties for the manufacture of our product candidates for preclinical and clinical development and expect to continue to do so for the foreseeable future. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts. •~~ Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or any guidance we may provide. • We are dependent on the services of our management and other clinical and scientific personnel, and if we are not able to retain these individuals or recruit additional management or clinical and scientific personnel, our business will suffer. • Our success depends on our ability to protect our intellectual property and our proprietary technologies **, and if we are unable to protect our intellectual property and technologies, our business will suffer** . • The trading price of the shares of our common stock could be highly volatile, and purchasers of our common stock could incur substantial losses. **• Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.** Item 1. Business Business ~~Overview~~ **overview** We are a clinical- stage pharmaceutical company focused on the discovery, development and commercialization of novel therapeutics for endocrine diseases and endocrine- related tumors. Endocrine pathways function to maintain homeostasis and commonly use peptide hormones acting through G protein coupled receptors, or GPCRs, to regulate many aspects of physiology **,** including growth, energy, metabolism, gastrointestinal function and stress responses. We have built a highly productive drug discovery and development organization with extensive expertise in endocrine GPCRs. We have discovered a pipeline of oral nonpeptide (small molecule) new chemical entities that target peptide GPCRs to treat a variety of rare endocrine diseases where treatment options have significant efficacy, safety and / or tolerability limitations. Our product candidates include paltusotine (formerly CRN00808), which is in clinical development for the treatment of acromegaly and **carcinoid syndrome associated with** neuroendocrine tumors ~~complicated by carcinoid syndrome~~ , ~~CRN04777~~ **or NETs, and CRN04894** , which is in clinical development for congenital ~~hyperinsulinism~~

adrenal hyperplasia , ~~or HI, and CRN04894, which is in clinical development for~~ **or CAH** ~~diseases of excess adrenocorticotrophic hormone~~ , **and** ~~or ACTH, including~~ Cushing' s disease ~~and congenital adrenal hyperplasia, or CAH~~ . We are advancing additional product candidates through preclinical discovery and development studies in parallel. Our vision is to build ~~the leading~~ **a premier, fully integrated** endocrine **- focused pharmaceutical** company ~~which~~ **that** consistently pioneers new therapeutics to help patients better control their disease and improve their daily lives. We focus on the discovery and development of oral nonpeptide therapeutics that target peptide GPCRs with well **-** understood biological functions, validated biomarkers and the potential to substantially improve the treatment of endocrine diseases and ~~/ or~~ endocrine- related tumors. Our pipeline consists of the following product candidates: Paltusotine (SST2 Agonist Program) Paltusotine, our lead product candidate, establishes a new class of oral selective nonpeptide somatostatin receptor type 2, or SST2, agonists designed for the treatment of acromegaly and ~~neuroendocrine tumors, or~~ **carcinoid syndrome associated with** NETs. Somatostatin is a neuropeptide hormone that broadly inhibits the secretion of other hormones, including growth hormone, or GH, from the pituitary gland. Acromegaly arises from a benign pituitary tumor that secretes excess GH that, in turn, causes excess secretion of insulin- like growth factor- 1, or IGF- 1, by the liver. This loss of homeostasis in the GH axis results in excess tissue growth and other adverse metabolic effects throughout the body. **We estimate that** ~~Approximately~~ **approximately** 27, 000 people in the United States suffer from acromegaly, and depending on surgical success, we estimate that approximately 11, 000 are candidates for chronic pharmacological intervention, of which somatostatin peptide analogs are the primary pharmacotherapy. **Carcinoid syndrome occurs when** NETs **, which** originate from neuroendocrine cells commonly found in the gut, lung or pancreas ~~. Typically , NETs are only diagnosed at a time of extensive metastatic disease and will often progress to liver failure~~ **secrete hormones or other chemical substances into the bloodstream that cause severe flushing or diarrhea, among other symptoms** . NETs are present in approximately 175, 000 adults in the United States. Of these, it is estimated that approximately 33, 000 patients have carcinoid syndrome ~~, which occurs when the tumors secrete hormones or other chemical substances into the bloodstream that cause severe flushing or diarrhea, among other symptoms. While still an orphan disease, NETs are the second most common gastrointestinal malignancy after colon cancer~~ . Most NETs overexpress SST2 receptors and injected depots of peptide somatostatin analogs have become the first- line standard of care ~~for many NETs patients~~ as detailed in National Comprehensive Cancer Network, or NCCN, guidelines. In ~~2022~~ **2023** , branded **injected** somatostatin peptide drugs accounted for approximately $ 2. ~~8~~ **5** billion in global sales for the treatment of acromegaly, NETs **,** and other uses. These drugs require painful monthly or daily injections and, in the case of somatostatin peptide drugs, often fail to fully control the disease in many acromegaly **or carcinoid syndrome** patients. The U. S. Food and Drug Administration, or FDA, has granted orphan drug designation for paltusotine for the treatment of acromegaly. To date, **our** ~~we have conducted multiple Phase 1 and Phase 2~~ clinical trials ~~and results~~ have shown that paltusotine was generally well tolerated **among healthy adults and patients with both** ~~. In our ACROBAT Phase 2 program in~~ acromegaly ~~patients, including in our ACROBAT Advance long- term extension study, paltusotine maintained IGF- 1 levels in patients previously treated with injected somatostatin receptor ligands, or SRLs, in which paltusotine lowered~~ and **carcinoid syndrome** ~~maintained IGF- 1 for up to 103 weeks at levels comparable to prior injected SRL therapy~~ . **Our** ~~We are currently conducting a~~ Phase 3 development program for paltusotine in acromegaly ~~which~~ consists of two placebo- controlled clinical trials **, PATHFNDR- 1 and PATHFNDR- 2** . The ~~first of these, the~~ PATHFNDR- 1 trial **was** ~~, is~~ designed as a double- blind, placebo- controlled, nine- month clinical trial of paltusotine in acromegaly patients with average IGF- 1 levels less than or equal to 1. 0 times the upper limit of normal, or ULN, and who ~~are~~ **had been** on stable doses of somatostatin receptor ligand monotherapy (octreotide LAR or lanreotide depot). We are also conducting a second study, the PATHFNDR- 2 trial, which is designed as a double- blind, placebo- controlled, six- month clinical trial of acromegaly patients with elevated IGF- 1 levels. **Three groups of subjects have been enrolled in PATHFNDR- 2, including subjects who are treatment- naive (Group 1), subjects not receiving medical therapy and who last received medical therapy at least four months prior to screening (Group 2), and subjects who are controlled on octreotide or lanreotide but agree to washout prior to beginning study treatment (Group 3). Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The PATHFNDR- 2 study population was stratified to ensure equivalent active treatment versus placebo allocations in each stratum. We originally planned to enroll approximately 76 subjects based on the assumption that there would be an equal number of subjects in each stratum. Due to higher than expected enrollment of naïve patients, we increased the targeted sample size to 98 patients in order to ensure sufficient statistical power to detect a difference between the active and placebo groups for the study as a whole and to increase experience with paltusotine in naïve and untreated patients. The sample size adjustment was prespecified in the protocol if enrollment in Stratum 2 was below a predetermined threshold.** The primary endpoint of both PATHFNDR studies **is** ~~will be~~ the proportion of patients with IGF- 1 ≤ 1. 0 × ULN at the end of the treatment period on paltusotine as compared to placebo. ~~Enrollment in~~ **Positive topline data from the randomized controlled portion of the** PATHFNDR- 1 **study was reported in September 2023, where the primary endpoint and all secondary endpoints of the study were achieved. The study met statistical significance (p < 0. 0001) on the primary endpoint, based on the proportion of participants whose IGF- 1 levels were maintained ≤ 1. 0 × ULN in the paltusotine arm (83 %) compared to those in the placebo arm (4 %). All secondary endpoints also met statistical significance. In the PATHFNDR- 1 study, paltusotine was well tolerated and no serious or severe adverse events were reported in participants treated with paltusotine. The frequency of participants with at least one treatment emergent adverse event, or TEAE, was comparable in the paltusotine treatment arm vs placebo, or PBO arm (80 % vs. 100 % respectively). The most commonly reported TEAEs in paltusotine included: arthralgia (27 % paltusotine vs. 57 % PBO), headache (20 % paltusotine vs. 36 % PBO), diarrhea (23 % paltusotine vs. 14 % PBO), abdominal pain (17 % paltusotine vs. 11 % PBO) and nausea (10 % paltusotine vs. 7 % PBO). The frequency of adverse events considered related to acromegaly was notably lower in paltusotine treated participants compared to placebo treated participants (30 % vs. 86 % respectively). The open label extension phase of the PATHFNDR- 1 trial is ongoing. Enrollment in the**

PATHFNDR- 2 study was completed in **August** ~~2022~~ **2023** ~~,~~ and ~~we~~ **a total of 112 subjects were randomized and a total of 111 subjects were enrolled who were either treatment- naïve (n = 46) or untreated for at least four months (n = 36), or who washed out of prior octreotide or lanreotide monotherapy [(n = 29)]. We** expect topline data from the PATHFNDR- ~~1 study in the third quarter of 2023. Enrollment in the PATHFNDR-~~ 2 study ~~is ongoing and, based on our current projections, we expect topline data~~ in **March** ~~the first quarter of~~ 2024. We believe that, if successful, the two trials could support **global** marketing applications for the use of paltusotine for all acromegaly patients who require pharmacotherapy, including untreated patients and those switching from other therapies, and we would plan to seek regulatory approval for paltusotine for the treatment of acromegaly in the United States with an anticipated submission of a New Drug Application, or NDA, **to the FDA** in **the second half of** 2024 **with the potential for approval in 2025** . We are also conducting a **randomized, open- label, parallel group, multi- center** Phase 2 ~~trial~~ **study** to assess the safety **,** and pharmacokinetics of **multiple doses of** paltusotine in **people living with carcinoid syndrome. In addition, exploratory efficacy during the 8- week period will be evaluated including frequency of bowel movements and flushing episodes. Participants were randomized to receive either 40 mg or 80 mg of paltusotine, with the ability to dose titrate based on tolerability or inadequate control of symptoms during the first four weeks of treatment. Enrollment in the study is complete, with a total of 36 participants enrolled. We reported positive initial data from our ongoing open- label Phase 2 carcinoid syndrome study in December 2023 and topline data from the complete study is expected in the first half of 2024. In December 2023, safety data were available for 27 participants, 23 of whom had completed at least two weeks of the randomized treatment period and 15 of whom had completed the full 8- week randomized treatment period. The initial findings indicated that: • Administration of paltusotine resulted in rapid and sustained reductions in bowel movement, or BM, frequency and flushing episodes: o65 % reduction of excess BMs (defined as daily bowel movements above the upper limit of normal, 3 / day) for** patients with ~~NETs complicated by~~ **> 3 / day at baseline o65 % reduction of flushing frequency for patients with > 1 / day at baseline • Exposure of paltusotine in people with** carcinoid syndrome **was consistent** ~~. We expect data from this study in the second half of 2023. In February 2022, we entered into a license agreement~~ with **prior clinical studies •** ~~Sanwa Kagaku Kenkyusho Co., Ltd., or Sanwa, pursuant to which Sanwa has the exclusive right to develop and commercialize paltusotine~~ **Paltusotine** ~~in Japan,~~ **was generally well-tolerated with a safety profile consistent with prior clinical studies oThere were no treatment- related severe** or **serious adverse events, or AEs, with** the ~~Sanwa License~~ **majority of treatment- related AEs being mild- to- moderate. oThe most frequently reported AEs included diarrhea, headache, and abdominal pain** . CRN04894 (ACTH Antagonist) CRN04894 is our investigational, oral, nonpeptide product candidate designed to antagonize the **adrenocorticotrophic hormone, or** ACTH **,** receptor, intended for the treatment of diseases caused by excess ACTH, including **CAH and** Cushing' s disease ~~and CAH. Cushing' s disease results from a pituitary tumor that secretes excess ACTH which, in turn, causes the downstream synthesis and over- secretion of cortisol by the adrenal glands. Cortisol is the body' s main stress hormone and excess amounts can cause significant increases in mortality and morbidity~~ . CAH encompasses a set of disorders that are caused by genetic mutations that result in impaired cortisol synthesis. A lack of cortisol leads to a ~~loss~~ **breakdown** of feedback mechanisms and results in persistently high levels of ACTH, which, in turn, causes overstimulation of the adrenal cortex. The resulting adrenal hyperplasia and over- secretion of other steroids (particularly androgens) and steroid precursors can lead to a variety of effects from improper gonadal development to life- threatening dysregulation of mineralocorticoids. ~~In~~ **Cushing' s disease results from a pituitary tumor that secretes excess ACTH which, in turn, causes** the ~~United States~~ **downstream synthesis and over-secretion of cortisol by the adrenal glands. Cortisol is the body' s main stress hormone and excess amounts can cause significant increases in mortality and morbidity. Based on genetic incidence rates** , there are an estimated 27, 000 patients with CAH and over 11, 000 patients with Cushing' s disease **in the United States** . Of the patients with CAH and Cushing' s disease, we estimate that 17, 000 and 5, 000 patients, respectively, are potential candidates for treatment with CRN04894. We conducted a double- blind, randomized, placebo- controlled Phase 1 study of CRN04894 in healthy volunteers to assess the safety and tolerability of single and multiple doses of CRN04894. In addition, the study was designed to measure the effect of CRN04894 on suppression of cortisol, cortisol precursors, and adrenal androgens following exogenous ACTH stimulation. ~~We~~ **In May 2022, we** announced positive topline data from the Phase 1 study ~~.~~ **which showed** CRN04894 was well tolerated and demonstrated dose- dependent increases in CRN04894 plasma concentrations. We believe CRN04894 demonstrated pharmacologic proof- of- concept, as the Phase 1 results showed **dose- dependent** reductions of both basal cortisol and elevated cortisol following an ACTH challenge. All adverse events were considered mild to moderate and there were no serious adverse events. In **January 2023, we submitted an Investigational New Drug application, or IND, to** the ~~fourth~~ **FDA for the study of CRN04894 in CAH. In February 2023, we initiated a Phase 2 study in CAH patients. This open- label, Phase 2, study is designed to evaluate the safety, efficacy, and pharmacokinetics of different doses of CRN04894. In addition, biomarkers, including serum androstenedione and 17 hydroxyprogesterone, will be measured as we seek to evaluate the potential efficacy of CRN04894. Initial data from this Phase 2 study is expected in the second** quarter of **2024. In September** 2022, we entered into a Clinical Trial Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, of the National Institutes of Health, or NIH, to collaborate on a company- sponsored multiple- ascending dose ~~exploratory~~ trial of CRN04894 in ACTH dependent Cushing' s Syndrome, or ADCS. ADCS includes patients with either Cushing' s disease or Ectopic ACTH Syndrome, or EAS. This open- label study is designed to evaluate safety **, tolerability,** and pharmacokinetics of ~~increasing~~ **different** doses of CRN04894 in patients with ADCS as well as to measure 24- hour urinary-free cortisol and serum cortisol as indicators of efficacy. **The** ~~Study activities for this~~ study ~~have begun~~ **is enrolling patients** and **, based on our current projections, initial** data is expected from the study in **the first half of** 2024 ~~. In January 2023, we submitted an Investigational New Drug application, or IND, to the FDA for the study of CRN04894 in CAH. In February 2023, we were notified that the IND was allowed to proceed, and we have initiated study activities for a Phase 2 study in CAH patients. This open- label Phase 2 study is designed to evaluate the safety and pharmacokinetics of increasing doses of~~

~~CRN04894. In addition, biomarkers, including serum androstenedione and 17 hydroxyprogesterone, will be measured as we seek to evaluate the potential efficacy of CRN04894. Data from this Phase 2 study is expected in 2024. CRN04777 (SST5 Agonist) CRN04777 is our investigational, oral, nonpeptide somatostatin receptor type 5, or SST5, agonist designed for the treatment of congenital hyperinsulinism, or HI. Congenital HI is a devastating rare genetic disease associated with dysregulated insulin production, in which excess insulin produces life- threatening hypoglycemia (low blood glucose) beginning at birth. This loss of homeostatic control of blood glucose levels can lead to seizures, developmental disorders, learning disabilities, coma and even death. Congenital HI occurs in approximately 1 in 25, 000 to 50, 000 new births in the United States. Approximately 2, 200 patients in the United States are diagnosed with Congenital HI, and depending on surgical success, we estimate that approximately 1, 500 are candidates for chronic pharmacological intervention. We have completed a double- blind, randomized, placebo- controlled Phase 1 study of CRN04777 in healthy volunteers to assess the safety and tolerability of single and multiple doses of CRN04777. In addition, the study was designed to evaluate the potential mechanism of action of CRN04777 by measuring the suppression of insulin secretion in healthy volunteers following stimulation with either glucose or a sulfonylurea, agents that increase the secretion of insulin. We announced positive topline data from the single ascending dose, or SAD, cohorts and the multiple ascending dose, or MAD, cohorts and we believe CRN04777 demonstrated pharmacologic proof- of- concept, based on potent suppression of stimulated insulin observed in these subjects. The plasma exposure of CRN04777 suggested the drug was well absorbed with a half- life of approximately 40 hours, which we believe supports the potential for once daily administration in patients. All adverse events were considered mild or moderate and there were no serious adverse events. CRN04777 was well tolerated at single and multiple doses from 0. 5 mg up to 120 mg and exhibited dose- proportional pharmacokinetics for the same dose range. A dose- dependent reduction in glucose- induced insulin secretion was demonstrated with an intravenous glucose tolerance test in the SAD cohorts and a dose- dependent reversal of sulfonylurea- induced insulin secretion was seen in both the SAD and MAD cohorts. The sulfonylurea- induced insulin secretion model represents a pharmacologic analog of the hyperinsulinism that many patients experience. Following the completion of the adult healthy volunteer study under a Clinical Trial Application in Germany, in October 2022, we submitted an IND to the FDA to initiate the first U. S. clinical study of CRN04777, which is designed to evaluate the compound in a pediatric population (ages 3 months to 12 years). In November 2022, the FDA informed us that the IND was placed on clinical hold and the proposed Phase 2 clinical study may not yet be initiated. We are in the process of collecting additional information and data to submit to the FDA, with the goal of being allowed to proceed with the Phase 2 study in patients with congenital HI. The FDA has granted rare pediatric disease designation for CRN04777 for the treatment of congenital HI. The European Medicines Agency, or EMA, has granted orphan drug designation for CRN04777 for the treatment of congenital HI and the United Kingdom Medicines and Healthcare products Regulatory Agency, or MHRA, has granted CRN04777 an Innovation Passport for the treatment of congenital HI. We also expect CRN04777 can be broadly developed for the treatment of other diseases characterized by excess insulin secretion, including forms of syndromic hyperinsulinism, of which there are an estimated 1, 700 patients in the United States~~ . Parathyroid Hormone Antagonist We are developing antagonists of the parathyroid hormone, or PTH, receptor for the treatment of primary hyperparathyroidism, or PHPT and humoral hypercalcemia of malignancy, or HHM, and other diseases of excess PTH. PTH regulates calcium and phosphate homeostasis in bone and kidney through activation of its receptor, PTHR1. Increased activation of PTHR1, either via PTH or PTH- related peptide (PTHrP, PTHLH) can lead to skeletal, renal, gastrointestinal, and neurological problems. Primary hyperparathyroidism arises from a small, benign tumor on one or more of the parathyroid glands, which results in over- secretion of PTH, leading to increased blood calcium levels, or hypercalcemia. Some patients experience no symptoms, and many can have surgery to remove the tumor and / or hyperactive gland (s), while some require management with medical therapy. Symptomatic PHPT is characterized by skeletal, renal, gastrointestinal, and neurological manifestations with increased mortality. HHM typically arises in patients with advanced- stage cancers. In cases of HHM, over-secretion of PTHrP caused by the malignant tumor results in bone resorption and calcium reabsorption in the kidney, leading to hypercalcemia. We have identified investigational, orally available nonpeptide PTH antagonists that showed activity and drug-like properties in preclinical models. We are evaluating a subset of molecules to identify potential development candidates that we believe are suitable for evaluation in human clinical trials, and we expect to select a development candidate in **the first half of ~~2023~~ 2024** . **~~Radioneties Oncology~~ SST3 Agonist Program for the Treatment for Autosomal Dominant Polycystic Kidney Disease We have identified investigational** , **~~Inc. On October 18~~ orally available somatostatin receptor type 3** , **~~2021~~ or SST3** , **targeted nonpeptide agonists for the treatment of Autosomal Dominant Polycystic Kidney Disease, or ADPKD. ADPKD, which is the most frequent genetic cause of chronic kidney disease, affecting 1 in 1, 000 individuals, and is the fourth leading cause of end- stage renal disease. Cyst formation in renal tubules results from mutations in either the PKD1 or PKD2 genes. Over time, these developing cysts destroy the kidney architecture and impair kidney function. Cyst formation raises ciliary adenylyl cyclase activity and increases cAMP levels, which is central to the establishment of the disease. SST3 is expressed in cyst lining cells in ADPKD patients and inhibits cAMP formation within the cilia upon activation. Therefore, a selective SST3 agonist could provide a new avenue to prevent cyst formation and growth. We are evaluating a subset of nonpeptide SST3 agonists to identify potential development candidates that** we **believe will be suitable for evaluation in human clinical trials. We expect to select a development candidate in the first half of 2024. Thyroid Stimulating Hormone Receptor Antagonist We are developing thyroid-stimulating hormone receptor** , **~~together~~ or TSHR, antagonists for the treatment of Graves' disease and Thyroid Eye Disease, or TED, or Grave' s orbitopathy. Graves' disease is an autoimmune condition that affects approximately 1 in 100 people in the United States and 2- 3 % of the population worldwide. It is characterized by the production of autoantibodies against TSHR, and the pathology of Graves' disease is driven by these TSHR stimulatory antibodies, or TSAb, that result in heightened activation of TSHR. This overstimulation results in hyperthyroidism due to excessive production of thyroid hormones. Approximately 30 % of Graves' disease patients also develop TED due to**

overactivation of TSHR in orbital fibroblasts leading to excessive production of hyaluronic acid, adipogenesis, cytokine production, and fibrosis. This causes a constellation of debilitating symptoms including pain, swelling, blurry vision, diplopia, and proptosis. Several long- standing treatments for Graves' hyperthyroidism are available including anti-thyroid drugs, radioactive iodine, or RAI, and surgery. RAI and surgery are definitive treatments for Graves' hyperthyroidism, but often result in hypothyroidism. In addition, none of the current treatments for Graves' hyperthyroidism are effective in treating TED and, in some cases, such as with ~~5AM Ventures~~ **RAI, the treatments worsen the condition. Blocking TSHR activation directly via a TSHR antagonist may provide** ~~and~~ **an important new therapeutic mechanism** ~~Frazier Healthcare Partners, announced the formation of Radionetics Oncology, Inc., or Radionetics. Radionetics aims~~ to ~~develop a deep pipeline of novel~~ **treat patients with Graves' disease that would effectively treat both the hyperthyroidism and TED. We have identified investigational** , ~~targeted,~~ **orally available** nonpeptide ~~radiopharmaceuticals~~ **TSHR antagonists that demonstrate activity in preclinical models and possess good and drug- like properties. We are evaluating a subset of molecules to identify potential development candidates that we believe will be suitable** for **evaluation in human clinical trials** ~~the treatment of a broad range of oncology indications. In connection with the formation of Radionetics~~ , **and** we **expect** ~~entered into a Collaboration and License Agreement with Radionetics, or the Radionetics License, granting Radionetics an exclusive world- wide license~~ to **select a** ~~our technology for the~~ development **candidate** ~~of radiotherapeutics and related radio- imaging agents~~ in **2024** ~~exchange for a majority equity stake in Radionetics, a warrant to obtain additional shares of common stock of Radionetics, potential sales milestones in excess of $ 1. 0 billion and single- digit royalties on net sales~~ . Research Discovery Patients with many other debilitating endocrine diseases **and endocrine related tumors** await new therapeutic options, and we ~~are~~ continuously ~~evaluating~~ **evaluate and prioritize** where to ~~next~~ deploy our drug discovery efforts. We plan to continue to expand our drug discovery efforts and leverage our expertise in the evaluation of additional ~~conditions~~ **unmet medical needs. In addition to our programs for hyperparathyroidism, ADPKD, and Graves' Disease (** including **TED)** ~~polycystic kidney disease~~ , **we are evaluating potential product candidates for** metabolic diseases (including diabetes and obesity) ~~and Graves' Disease (including Thyroid Eye Disease)~~ , ~~among other~~ **and GPCR- targeted oncology** indications. All of our product candidates have been discovered, characterized and developed internally and are the subject of composition of matter patent applications. We ~~have retained worldwide rights to commercialize our product candidates and~~ do not have any royalty obligations **and have retained worldwide rights to commercialize our product candidates,** except with respect to the exclusive right to develop and commercialize paltusotine in Japan pursuant to the Sanwa License, ~~and~~ the exclusive right to our radiotherapeutics technology pursuant to the Radionetics License **(as defined below), and the exclusive right to develop and commercialize CRN01941, a separate SST2 agonist licensed to Cellular Longevity Inc., doing business as Loyal, for veterinary use, or the Loyal License. Radionetics Oncology, Inc. On October 18, 2021, we, together with 5AM Ventures and Frazier Healthcare Partners, announced the formation of Radionetics Oncology, Inc., or Radionetics. Radionetics aims to develop a deep pipeline of novel, targeted, nonpeptide radiopharmaceuticals for the treatment of a broad range of oncology indications. In connection with the formation of Radionetics, we entered into a Collaboration and License Agreement with Radionetics, or the Radionetics License, granting Radionetics an exclusive world- wide license to our technology for the development of radiotherapeutics and related radio- imaging agents in exchange for an equity stake in Radionetics, a warrant, or the Radionetics Warrant to purchase additional shares of common stock of Radionetics, potential sales milestones in excess of $ 1. 0 billion and single- digit royalties on net sales. In August 2023, we exercised the Radionetics Warrant to purchase 3, 407, 285 shares of Radionetics common stock with an exercise price of $ 0. 00001 per share and invested $ 5. 0 million to purchase 14, 404, 656 shares of preferred stock in Radionetics along with new and existing investors who participated in the transaction. Subsequent to the Radionetics Warrant exercise, we exchanged 60 % of our total number of outstanding shares of Radionetics common stock for 32, 344, 371 shares of Radionetics preferred stock on a one- for- one basis. Additionally, in August 2023, the Radionetics License was amended to include additional sales milestones of up to $ 15. 0 million. Following the amendment to the Radionetics License, we are eligible to receive total potential sales milestones in excess of $ 1. 0 billion and single- digit royalties on net sales. In December 2023, Radionetics also completed a financing to sell additional shares of preferred stock to other investors. As a result, as of the year ended December 31, 2023, we have an approximately 26 % ownership stake in Radionetics consisting of common and preferred stock (see" Note 9" to the consolidated financial statements)** . Our strategy Our objective is to transform the treatment of endocrine diseases and endocrine- related tumors by creating a diversified portfolio of novel therapeutics that will advance the standard of care. To achieve this objective, we are pursuing the following strategy: • Focus on endocrine diseases and endocrine- related tumors with significant unmet medical need. There are numerous endocrine diseases and endocrine- related tumors for which currently available pharmacological therapies (when they exist) have significant limitations in efficacy, safety and / or tolerability. Patients living with these diseases often experience significant morbidity, mortality and / or poor quality of life. We are focused on discovering, developing, and commercializing orally available therapies for multiple indications across endocrinology to advance the standard of care for these patients. • Rapidly advance multiple product candidates in parallel to clinical proof- of-concept and late- stage development by targeting diseases that ~~require relatively small trials and~~ employ validated biomarkers as clinical endpoints. Phase 1 clinical trials for endocrine diseases and endocrine- related tumors can often measure predictive biomarkers in healthy volunteers and lower the technical risk by providing a predictive measure of efficacy early in clinical development. ~~Clinical trials in these indications often enroll relatively small numbers of trial subjects and use validated biomarkers as registration endpoints, which we believe will allow us to efficiently develop multiple clinical programs in parallel.~~ • Continue to expand our therapeutic pipeline for endocrine diseases **and endocrine- related tumors** by leveraging the capabilities of our experienced discovery team in the area of peptide hormone GPCRs. Our discovery team has significant expertise in understanding and creating product candidates to influence the dynamic behavior of GPCRs and has developed a

number of proprietary methods, techniques and tools that we believe will enable us to efficiently and reliably evaluate newly synthesized molecules. We employ an iterative strategy where compounds are designed, synthesized, and rapidly characterized for pharmacologic and pharmaceutical properties. This approach has led to our current pipeline, and we will continue to invest in creating additional product candidates acting at this important class of targets. Peptide hormone GPCRs regulate many aspects of physiology and are attractive drug targets for treating a broad range of diseases. There are more than 80 known peptide hormones acting at more than 120 known different receptors. With each of our drug discovery programs, our goal is to specifically tailor a product candidate with pharmacologic and pharmaceutical properties highly optimized for its interaction with its specific GPCR target that we anticipate will translate to downstream benefits in our chosen therapeutic applications. • Retain significant development and commercial rights to our product candidates. We intend to commercialize our product candidates if approved by regulators. In February 2022, we entered into the Sanwa License pursuant to which Sanwa has the exclusive right to commercialize paltusotine in Japan. In the future, we may enter into additional distribution or licensing arrangements for commercialization rights for other product candidates. • Maintain an entrepreneurial, scientifically rigorous, and inclusive corporate culture where employees are fully engaged and strive to bring improved therapeutic options to patients. The patients we seek to treat currently ~~only~~ have **limited treatment** options with significant drawbacks and often limited efficacy, safety and / or tolerability. We are passionate about developing new pharmacological therapies to help these patients better control their diseases and to reduce the impact of these diseases on their daily lives. We believe that building a successful and sustainable endocrine company requires not just specific expertise in multiple areas of drug discovery, development, and commercialization, but a team- oriented culture that integrates and harnesses the creative energy, scientific insights and ~~enthusiasm~~ **passion** of the entire organization. The endocrine system **Overview** The endocrine system regulates most of the body' s physiological activities through the actions of hormones, which are chemical and biochemical messengers secreted from different organs that influence growth, gastrointestinal function, maturation and development, reproduction, stress, metabolism and nearly all aspects of homeostasis. Hormones are structurally variable and can be monoamines, steroids, amino acids, peptides, or larger proteins. The endocrine system includes, among other glands and organs, the pituitary gland, hypothalamus, pancreas, adrenal gland, thyroid and parathyroid, ovaries and testes, as well as specialized enteroendocrine cells. Hormonal secretion is complex, and the body employs several mechanisms to exert positive and negative feedback control to maintain homeostasis. For example, the pituitary gland, which is located behind the eyes at the base of the brain, is sometimes referred to as " the master endocrine gland " because it regulates multiple endocrine systems. Positive and negative control of pituitary hormonal secretion is often dictated by the adjacent hypothalamus, which integrates feedback responses from other areas of the body, including the brain. In the case of GH, its synthesis and secretion are stimulated by growth hormone- releasing hormone, or GHRH, and inhibited by somatostatin, which are both hypothalamic peptides. Another example is the pancreas that secretes insulin and glucagon, which lower and raise blood glucose levels, respectively. Insulin and glucagon secretion are both inhibited by somatostatin, which is also locally produced in and secreted by specific cells in the pancreas. Hormonal dysregulation can arise from endocrine organ defects, including injury, inflammation, genetic abnormalities, or the growth of tumors derived from endocrine cells. These insults can result in the under- secretion or over- secretion of one or more hormones, disrupting homeostasis and causing disease. For example, several serious clinical disorders, including acromegaly and Cushing' s disease, result from pituitary tumors secreting excess hormones. ~~In the pancreas, genetic defects or cellular dysfunction can give rise to disorders of under- secretion or over- secretion of pancreatic hormones (e. g., hyperinsulinemia).~~ Various GPCRs are expressed in every type of cell in the body and their function is to transmit signals from outside the cell across the membrane to signaling pathways within the cell, between cells and between organ systems. Because of these critical actions, the GPCR superfamily is the largest and single most important family of drug targets as highlighted by the large number of approved therapeutics targeting this class. However, most currently available GPCR- targeting drugs act ~~at~~ **as** receptors for which the native ligands are small molecules, such as histamine, adrenaline, and neurotransmitters. Most peptide hormones bind selectively to specific receptors located on the surface of cells in the target tissue. Receptors for peptide hormones are often GPCRs, which play a central role in many biological processes and are linked to a wide range of disease areas. There are more than 80 known peptide hormones acting at more than 120 known different receptors. Historically, it was assumed that small molecules could not replicate or compete with the complex interactions between peptides and their cognate GPCRs. As such, most drugs developed for peptide GPCRs have been and continue to be peptides themselves, which present manufacturing and formulation difficulties and force patients to undergo frequent injections because peptides generally are not orally bioavailable. We believe our approach to developing novel small molecule product candidates that uniquely engage peptide hormone GPCRs will enable us to generate orally bioavailable, and potentially more selective, effective and better tolerated therapeutics for patients. The somatostatin receptor family of peptide GPCRs is an illustrative example of the complex and subtle control inherent in endocrine biology and peptide hormone physiology. The peptide hormone somatostatin, which was first isolated over 40 years ago, is produced by a variety of cell types and has pleiotropic effects throughout the body, many of which are related to the inhibition of secretion of other hormones or neurotransmitters, and selective activation of this activity has made somatostatin agonism a well- established, commercially validated mechanism. These effects are mediated by five different somatostatin receptor proteins (SST1, SST2, SST3, SST4, and SST5), which lower levels of cyclic adenosine monophosphate, or cAMP, a key intracellular signaling molecule regulated by GPCR activation. Each of these receptors is expressed in different subsets of tissues. For example, SST2 is the most widely expressed subtype in NETs and is the dominant receptor by which GH secretion is suppressed in the pituitary. ~~The SST5 receptor is expressed by pancreatic islet cells where its activation potently inhibits insulin secretion.~~ GPCRs were originally thought to function as simple on- off switches responding to hormones and neurotransmitters but have since been shown to exhibit complex and diverse molecular and cellular behaviors. Many lines of structural and mechanistic research demonstrate that distinct signaling cascades and feedback mechanisms create multi- dimensional pathways with distinct physiological responses. These different responses are based on ligand binding kinetics, receptor regulation and trafficking

~~(Figure 1)~~. Some transduce signals into the cell interior to regulate various cellular functions. Other responses attenuate hormonal signals to prevent overstimulation and include receptor internalization (a removal of the GPCR from the cell surface, which makes it unavailable for external ligands), desensitization and downregulation. The capacity of a GPCR ligand to preferentially affect one of these pathways, such as G- protein signaling, over others, such as receptor downregulation, is termed biased agonism We believe our understanding of these different signaling pathways enables us to develop oral, small molecule product candidates that not only are highly selective for specific receptor subtypes but also are further custom- tailored to activate specific GPCR properties and ultimately improve patient outcomes. All of our product candidates have been discovered and developed internally and we have retained global rights to commercialize our product candidates and have no royalty or licensing obligations **, other than the Sanwa License discussed herein** . The following table summarizes our **current** product candidate pipeline **. Please see the " Business Overview " section above for additional information** . Somatostatin receptor type 2 agonists for the treatment of acromegaly and **carcinoid syndrome associated with** neuroendocrine tumors Our lead product, paltusotine, is an oral selective nonpeptide SST2 agonist in clinical development for the treatment of acromegaly **and carcinoid syndrome** . The FDA **has** granted orphan drug designation for paltusotine for the treatment of acromegaly. Results from our Phase 1 trial of paltusotine demonstrated initial clinical proof- of- concept based on observed suppression of GH and IGF- 1 secretion in healthy volunteers. In October 2020, we announced positive topline results from the ACROBAT Edge and Evolve Phase 2 trials in acromegaly. The prespecified primary endpoint in Edge was achieved, showing that once daily oral paltusotine maintained IGF- 1 levels at Week 13 in acromegaly patients who were switched from an injected somatostatin receptor ligand depot of either octreotide or lanreotide monotherapy. **Our** ~~We are currently conducting our~~ Phase 3 **development** program ~~of~~ **for** paltusotine in acromegaly ~~patients~~ **consists of two placebo- controlled clinical trials, PATHFNDR- 1** and **PATHFNDR- 2. Positive** topline data **from** ~~is expected in~~ the ~~second half~~ **randomized controlled portion** of **the PATHFNDR- 1 study was reported in September** 2023 ~~. We are also conducting a Phase 2 trial to assess the safety and pharmacokinetics of paltusotine in patients with NETs complicated by carcinoid syndrome~~ . We expect topline data from ~~this~~ **the PATHFNDR- 2** study in **March 2024. We are also conducting a Phase 2 study to assess** the ~~second~~ **safety and pharmacokinetics of paltusotine in patients with carcinoid syndrome. Positive initial findings from our ongoing open- label Phase 2 carcinoid syndrome study were reported in December 2023 and topline data from the complete study is expected in the first** half of ~~2023~~ **2024** . In February 2022, we entered into the Sanwa License pursuant to which Sanwa has the exclusive right to develop and commercialize paltusotine in Japan **, upon which we received a $ 13. 0 million upfront payment** . Acromegaly disease background Acromegaly is typically caused by a pituitary tumor that secretes excess GH. Pituitary tumors are generally benign adenomas that, in addition to GH secretion, also express membrane receptors for somatostatin. Increased GH secretion results in excess downstream secretion of IGF- 1 from the liver. GH and IGF- 1 promote tissue growth and have other metabolic effects throughout the body. The symptoms of acromegaly include abnormal growth of hands and feet and changes in shape of the bones that **may** result in alteration of facial features **as well as enlarged hands and feet** . Overgrowth of bone and cartilage and thickening of tissue can lead to arthritis, carpal tunnel syndrome, joint aches, enlarged lips, nose and tongue, deepening of voice due to enlarged vocal cords, sleep apnea due to obstruction of airways and enlargement of the heart, liver and other organs. Additional symptoms can include thick, coarse, oily skin, skin tags, excessive sweating and skin odor, fatigue and weakness, headaches, goiter, decreased libido, menstrual abnormalities in women and erectile dysfunction in men. As the tumor grows, it can impinge on the nerves in the optic chiasm leading to visual problems and potentially vision loss. Compression of the surrounding normal pituitary tissues can decrease production of other pituitary hormones, resulting in hypopituitarism. Acromegaly patients experience increased mortality rates, principally due to cardiovascular diseases (diabetes, hypertension), respiratory disease and cerebrovascular diseases. Acromegaly is often suspected when the patient exhibits enlargement of extremities and an alteration of facial features. Pituitary tumors are also often found during clinical workup for severe headaches, vision changes or incidentally on cranial imaging initiated for other reasons. Elevation of serum IGF- 1 levels confirms the suspicion of acromegaly, but a formal diagnosis requires lack of suppression of serum GH levels in response to an oral glucose tolerance test. A magnetic resonance imaging (MRI) or computerized tomography (CT) scan of the pituitary is then used to locate the tumor, determine its size and assess the potential for surgical intervention. It is estimated that there are approximately 27, 000 patients in the United States with acromegaly, 11, 000 of whom we estimate are candidates for pharmacotherapy. Current acromegaly treatments and limitations The major goals of treatment are to reduce serum GH and normalize IGF- 1 levels, ameliorate symptoms and relieve any pressure resulting from the tumor. Surgical removal of the pituitary tumor is the first treatment option and often results in rapid improvement of symptoms. Surgery can be curative if the tumor is small and accessible enough to be fully resected. However, many acromegaly patients turn to pharmacological treatments if they are not candidates for surgery or surgery was unsuccessful. Somatostatin analogs octreotide (marketed as Sandostatin) and lanreotide (marketed as Somatuline) are selective for SST2 receptors and are the ~~preferred~~ first- line pharmacologic treatments. However, these peptides leave many patients inadequately controlled. For example, a meta- analysis published in 2014 by the Journal of Clinical Endocrinology and Metabolism showed that approximately 50 % of over 4, 000 acromegaly patients treated with octreotide or lanreotide failed to achieve biochemical control. Pegvisomant (marketed as Somavert) is a daily injectable GH receptor antagonist and is generally used in patients resistant to or intolerant of somatostatin analogs. Pasireotide (marketed as Signifor) is a less selective SST receptor agonist that is also used and has activity toward SST5, SST3 and SST2 receptors. However, pasireotide treatment leads to an increase in fasting plasma glucose levels in patients within the first two or three weeks of treatment and a pronounced shift to pre- diabetes and diabetes (as judged by HbA1c levels) within six months due to its insulin- suppressing SST5 activity. Orally administered dopamine agonists, such as cabergoline, are also used, but do not achieve hormone normalization in most patients. For this reason, dopamine agonists are usually used as adjunct to somatostatin analogs. While these currently approved drugs reduce the disease burden, many patients still report acromegaly symptoms despite treatment, particularly at the end of the monthly dosing

cycle. In 2020, octreotide capsules (marketed as MYCAPSSA) received marketing approval in the United States for long- term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide. Currently available therapies for acromegaly are primarily peptide drugs that require injection, making them both painful and inconvenient. Octreotide and pasireotide are typically a monthly intramuscular injection, lanreotide a monthly deep subcutaneous injection and pegvisomant a daily subcutaneous injection. Patients report pain, swelling and bruising both at the time of injection and for days following injections. In addition, octreotide, lanreotide and pasireotide labels require injections by a trained healthcare provider and are therefore inconvenient for patients. Finally, the reconstitution of octreotide and pasireotide can be complex and prone to error for healthcare providers. We believe that a once- daily oral nonpeptide somatostatin agonist that reduces excess GH secretion and normalizes IGF- 1 levels in acromegaly patients would represent a major clinical advance by eliminating painful injections and reducing the frequency of physician office visits. Additionally, we believe it should allow physicians to more quickly determine optimal dosing regimens compared to existing depot therapies. **Carcinoid syndrome** ~~Neuroendocrine tumors (NETs)~~ background NETs arise from cells of the enteroendocrine system in the gastrointestinal tract (approximately 70 % of cases) but can also arise from neuroendocrine cells in the lung (approximately 25 % of cases) or, more rarely, the pancreas. These tumors are usually slow growing and often initially asymptomatic. Therefore, many patients are only diagnosed at a time of extensive metastatic disease, and these patients can progress to liver failure. In approximately 19 % of cases, these tumors are associated with excess secretion of serotonin resulting in carcinoid syndrome, which is characterized by severe diarrhea and flushing. NETs are present in approximately 175, 000 adults in the United States, of which it is estimated that approximately 33, 000 patients have carcinoid syndrome ~~. While still an orphan disease, NETs are the second most common gastrointestinal malignancy after colon cancer.~~ Current ~~neuroendocrine tumor~~ **carcinoid syndrome** treatments and limitations Most NETs overexpress SST2 receptors and injected depots of peptide somatostatin analogs have become a standard of care for patients with carcinoid syndrome. While somatostatin analogs have been historically indicated primarily for patients with carcinoid syndrome, there is an evolving understanding of the positive impact of somatostatin analog treatment on the broader NETs patient population. For example, lanreotide was approved for the treatment of gastroenteropancreatic NETs based on a long- term study that showed significant improvement in progression free survival. However, many patients eventually become increasingly resistant to somatostatin analogs requiring increased dosage of depot preparations or use short- acting analogs as an add- on therapy. In 2017, the serotonin synthesis inhibitor, telotristat, was approved for the treatment of carcinoid syndrome diarrhea in combination with **injected** somatostatin ~~analog (SSA)~~ **receptor ligands, or SRLs,** therapy in adults inadequately controlled by ~~SSA~~ **SRLs** therapy. The overexpression of SST2 in NETs is also the basis for somatostatin targeted radioimaging of the tumors for diagnosis and staging. Peptide somatostatin analogs modified to incorporate a chelating agent can use their SST2 binding activity to concentrate radioisotopes in tumor tissue that can then be imaged using positron- emission tomography (PET). More recently, this approach has been adapted to deliver the beta particle emitter 177Lu for anti- tumor activity. A drug using this mechanism, Lutathera, significantly improved progression free survival and led to a substantial reduction in the risk of disease progression or death when added onto octreotide LAR therapy compared to a double dose of octreotide LAR, in a Phase 3 trial in NET patients who had failed on somatostatin analog therapy. Lutathera was approved in 2018 for the treatment of somatostatin receptor- positive gastroenteropancreatic **NETs** ~~neuroendocrine tumors~~ . Paltusotine overview and clinical development Paltusotine, our lead product candidate, ~~pioneers~~ **establishes** a new class of oral selective nonpeptide SST2 agonists designed for the treatment of acromegaly **and carcinoid syndrome associated with NETs** and is the first agent in its class with reported clinical results. It is designed to reduce excess GH secretion from benign pituitary tumors and normalize IGF- 1 levels in patients with acromegaly. In vitro pharmacology studies demonstrated that paltusotine potently stimulated SST2 receptor activity as measured by a decrease in cAMP accumulation in cells expressing the human SST2 receptor (EC50 = 0. 25 nM, the concentration that achieves 50 % cAMP inhibition). Analogous experiments using the other SST receptor subtypes showed paltusotine' s selectivity for SST2 was 4, 000 times greater than the other SST receptor subtypes. In addition to somatostatin receptor- directed pharmacology, paltusotine showed little off- target activity in a variety of assays for other GPCRs, enzymes, ion channels and transporters. Based on further in vivo studies in rats and dogs, paltusotine suppressed GH and IGF- 1 consistent with its mechanism of action. We conducted 28- day good laboratory practice, or GLP, toxicity studies in rats and dogs and identified no dose- limiting toxicities, which supported moving paltusotine into human clinical trials. We began a Phase 1, double- blind, placebo- controlled trial in late 2017 to assess the safety, tolerability, PK, and PD of paltusotine in 99 healthy human volunteers. This trial was performed at a single center in Melbourne, Australia. Subjects in the single ascending dose, or SAD, arm (up to 20 mg) were also evaluated for the ability of paltusotine to suppress GH secretion. Because GH secretion is pulsatile during the day, subjects in the first five SAD cohorts were given an intravenous bolus of GHRH (50 µg) to ensure a reliable window of high GH secretion. These GH responses were evaluated on day- 1 (the day prior to dosing) and again on day 1 (the day of dosing either paltusotine or placebo). The ability of paltusotine to suppress serum IGF- 1 was evaluated in the multiple ascending dose, or MAD, cohorts. Administration of GHRH on day- 1 resulted in a rapid surge of serum GH that lasted approximately 2 hours. In contrast to day- 1, the presence of paltusotine in plasma strongly suppressed (approximately 92 %) stimulated GH secretion, consistent with the compound' s activity as an SST2 agonist. This response was dose dependent. The first- generation paltusotine capsule achieved approximately 75 % of the total plasma exposure (area under the curve, or AUC) of the same dose administered as an oral solution to fasted subjects. However, when the capsule was administered with a standardized high fat meal, plasma AUC was reduced by approximately 83 %, suggesting that the first- generation capsule formulation should be taken under fasted conditions. In the drug- drug interaction cohort, repeated dosing of paltusotine resulted in no change in the exposure of the sensitive CYP3A4 reporter midazolam, suggesting that paltusotine is not likely to cause drug interactions by inhibiting the metabolism of other drugs that are primarily metabolized by the major CYP enzymes in the liver. In the MAD arm, subjects were dosed with paltusotine for seven days (5 mg cohort) or ten days (10- 30 mg cohorts) and serum IGF- 1 levels were measured each day. In both acromegaly patients and healthy volunteers, sustained

suppression of GH release results in lowering of serum IGF- 1 levels. However, in contrast to the rapid effects of the GH response, IGF- 1 levels are known to decrease more gradually and require several days of exposure to somatostatin agonists to produce an observable effect. As paltusotine concentrations reached steady state, serum IGF- 1 concentrations began to decline. This decline reached steady state in approximately seven days. Of note, IGF- 1 remained suppressed for several days after the final dose but began to recover as paltusotine plasma concentrations fell. Paltusotine exhibited a dose- dependent increase in exposure in the dose range of 5 mg to 30 mg and a terminal elimination half- life of 42 to 50 hours, consistent with potential for once daily administration. Suppression of IGF- 1 levels for the 10 mg, 20 mg and 30 mg cohorts was similar indicating that the 10 mg dose achieved a maximal response. This degree of IGF- 1 suppression by paltusotine was similar to that observed for peptide somatostatin analogs (octreotide, lanreotide) in previously reported healthy volunteer studies. Concentrations of somatostatin analogs in healthy volunteers that result in this level of suppression in healthy volunteers are comparable to the trough concentrations in patients on the highest approved dose. This suggests that drug concentrations that result in maximal suppression of IGF- 1 in healthy volunteers translates to meaningful suppression of IGF- 1 in acromegaly patients. The safety and tolerability of paltusotine in the trial was generally consistent with that of approved peptide somatostatin analogs. In the trial, paltusotine resulted in mild gastrointestinal disorders (such as abdominal pain, flatulence, abdominal distension, and diarrhea) in approximately 30 % of subjects and mild elevations of pancreatic enzymes in approximately 10 % of subjects. One subject experienced moderate abdominal pain after a single 40 mg dose. Additional adverse events included headache, dizziness and cardiac rhythm abnormalities (including nonsustained ventricular tachycardia, or NSVT) which were not dose dependent and also observed in placebo subjects and / or prior to dosing. One serious adverse event of moderate NSVT was observed following a single 1. 25 mg dose and was considered unlikely to be related to paltusotine. Based on the conclusions from this Phase 1 clinical study, we selected 10 mg as the initial dose for our Phase 2 trials. **Paltusotine in acromegaly patients** Following our Phase 1 study, we conducted global Phase 2 clinical trials with paltusotine in acromegaly patients. The first of these, Evolve, was a double- blind, randomized, placebo- controlled trial in patients whose IGF- 1 levels were biochemically controlled by octreotide or lanreotide monotherapy. We also conducted a second, open- label exploratory trial, Edge, to evaluate the effects of paltusotine on patients whose IGF- 1 levels were not biochemically controlled by octreotide or lanreotide alone. We are also conducting the Advance trial, which is a Phase 2 open label, long term extension study designed to evaluate the safety and efficacy of paltusotine in patients who completed the Evolve or Edge trials. We announced positive topline results from the ACROBAT Phase 2 program in acromegaly in October 2020. The prespecified primary endpoint in Edge was achieved, showing that once daily oral paltusotine maintained insulin- like growth factor- 1, or IGF- 1, levels at Week 13 in acromegaly patients who were switched from an injected ~~SRL~~ **SRLs**, depot of either octreotide or lanreotide monotherapy [change in IGF- 1 =- 0. 034 (- 0. 107, 0. 107), median (IQR)]. There were 25 patients enrolled in this prespecified primary analysis population (Group 1). During the four- week washout period after the 13- week treatment period, Group 1 patients showed a meaningful (> 20 %) and prompt (within two weeks) rise in IGF- 1 levels from baseline, which provided evidence regarding the magnitude of therapeutic activity of oral paltusotine in acromegaly patients. Edge also enrolled an additional 22 patients into four different exploratory populations (Groups 2- 5). As previously ~~announced~~ **disclosed**, the enrollment in Evolve was terminated early, enabling data to be available for the end of Phase 2 regulatory interactions on the Edge study. The reduced sample size did not allow for meaningful statistical comparisons between groups in the randomized withdrawal period. Data from these patients on lower doses of paltusotine were included in the post- hoc dose response analyses in combination with data from patients in the Edge study, most of whom received the higher doses. Post- hoc analyses of patients in Edge (Group 1; n = 25) and Evolve (n = 13) were conducted to explore the effect of paltusotine dose on IGF- 1 suppression. These analyses provided evidence of a dose response across the dose range of 10 to 40 mg. Dose- dependent results were observed when evaluating the effect on IGF- 1 levels from: 1) switching from injectable ~~SRL~~ **SRLs** to paltusotine, and 2) withdrawing paltusotine during the washout phase. These data and ongoing exposure response analysis has informed the selection of doses to be included the Phase 3 program. Paltusotine was generally well tolerated among the 60 ACROBAT participants (including both Edge and Evolve), which is consistent with prior clinical findings in healthy volunteers. There were no discontinuations due to drug- related adverse events, no safety signals seen in clinical laboratory analyses, no treatment- related SAEs, and no patients required rescue treatments with standard acromegaly medications during treatment. The most common treatment-emergent adverse events (> 10 %) included: headache, arthralgia, fatigue, peripheral swelling, paresthesia, and hyperhidrosis. **Paltusotine in people living** ~~Based on feedback from our interactions~~ with **carcinoid syndrome** ~~the FDA and other regulators, we have defined our Phase 3 development program which consists of two placebo- controlled clinical trials. We are conducting PATHFNDR- 1, which is designed as a double- blind, placebo- controlled, nine- month clinical trial of paltusotine in acromegaly patients with average IGF- 1 levels less than or equal to 1. 0 times the upper limit of normal, or ULN, and who are on stable doses of SRL monotherapy (octreotide LAR or lanreotide depot). The primary endpoint is the proportion of patients with IGF- 1 ≤ 1. 0 × ULN at the end of a nine- month treatment period on paltusotine as compared to placebo.~~ We are also conducting a ~~second~~ **randomized, open- label, parallel group, multi- center Phase 2** study **to assess the safety**, ~~PATHFNDR- 2~~ **and pharmacokinetics of multiple doses of paltusotine in people living with carcinoid syndrome. In addition**, **exploratory efficacy during the 8** ~~which is designed as a double- blind, placebo- controlled, twenty- four-~~ week **period** ~~trial in acromegaly patients with elevated IGF- 1 levels, who are untreated. Three groups of subjects~~ will be ~~enrolled~~ **evaluated** including ~~subjects~~ **frequency of bowel movements and flushing episodes. Participants were randomized to receive either 40 mg or 80 mg of paltusotine,** with **the ability** ~~no prior medical therapy (Group 1), subjects who last received medical therapy at least 4 months prior~~ to **dose titrate** ~~screening (Group 2), and subjects who are controlled on octreotide or lanreotide but agree to washout prior to beginning study treatment (Group 3). Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The study population will be stratified to ensure equivalent active treatment versus placebo allocations in each stratum. Approximately 76 subjects are planned to be enrolled~~ based on ~~the assumption that~~ **tolerability or inadequate**

control of symptoms during ~~there~~ -- **the first four weeks** ~~will be an equal number~~ of **treatment** ~~subjects in each stratum~~ . ~~If enrollment~~ **Enrollment** in ~~Stratum 2~~ **the study** is **complete** ~~below a prespecified threshold~~ , ~~the protocol allows for an increase in the sample size to ensure sufficient statistical power to detect a difference between the active and placebo groups. The primary endpoint in PATHFNDR- 2 is also the proportion of patients~~ with ~~IGF- 1 ≤ 1. 0 × ULN at the end of the treatment period on paltusotine as compared to placebo. A new tablet formulation of paltusotine is being used in both trials. When evaluated in~~ a **total of 36 participants enrolled** ~~Phase 1 pharmacokinetic healthy volunteer study, the tablet formulation had a reduced fasting requirement compared to the capsule formulation that was used in prior trials and dose proportional exposure was observed up to 80 mg~~ . **We reported positive initial** ~~Enrollment in PATHFNDR- 1 was completed in 2022 and we expect topline~~ data from **our** ~~the PATHFNDR- 1 study in the third quarter of 2023. Enrollment in the PATHFNDR- 2 study is~~ ongoing ~~and, based on our current projections, we expect topline data in the first quarter of 2024. We believe that, if successful, these trials could support marketing applications of paltusotine for all acromegaly patients who require pharmacotherapy, including untreated patients and those switching from other therapies, and we would plan to seek regulatory approval for paltusotine for We are also conducting an~~ open- label Phase 2 ~~trial to assess the safety and pharmacokinetics of paltusotine in patients with NETs complicated by~~ carcinoid syndrome ~~. We expect~~ **study in December 2023 and topline** data from ~~this~~ **the complete** study **is expected** in the ~~second~~ **first** half of ~~2023~~ **2024** . ACTH antagonists for the treatment of **Congenital Adrenal Hyperplasia,** Cushing' s disease ~~, Congenital, Adrenal Hyperplasia~~ , and other diseases of ACTH excess We are developing ~~,~~ CRN04894, an investigational, orally available nonpeptide ACTH antagonist, designed to block the action of adrenocorticotrophic hormone, or ACTH **, for CAH and Cushing' s disease** . CRN04894 is intended for the treatment of diseases caused by excess ACTH. ~~CRN04894 is currently in development for Cushing' s disease and CAH.~~ We have completed a Phase 1 study of CRN04894 in healthy volunteers **and** ~~, initiated~~ clinical studies **are ongoing** in patients with **CAH and** Cushing' s disease ~~and initiated study activities for a Phase 2 study in patients with CAH~~ . Background on diseases of ACTH excess CAH encompasses a set of disorders that are caused by genetic mutations that result in impaired cortisol synthesis.This lack of cortisol leads to a breakdown of feedback mechanisms and results in persistently high levels of ACTH,which in turn causes overstimulation of the adrenal cortex.The resulting adrenal hyperplasia and over- secretion of other steroids (particularly androgens) and steroid precursors can lead to a variety of effects from improper gonadal development to life- threatening dysregulation of mineralocorticoids.CAH is an orphan indication with **a** ~~an estimated~~ prevalence of approximately 27,000 patients in the United States **.** Cushing' s syndrome was first described by Harvey Cushing over a century ago and results from a prolonged exposure to elevated levels of glucocorticoids, particularly cortisol. Common signs include growth of fat pads (above the collarbone and on back of the neck), abdominal obesity, facial fat accumulation, excessive sweating, dilation of capillaries, thinning of the skin, muscle weakness, hirsutism, depression / anxiety, hypertension, osteoporosis, insulin resistance and hyperglycemia, heart disease and a range of other metabolic disturbances resulting in high morbidity. While excessive synthetic steroid administration or adrenal tumors can cause ACTH- independent forms of the disease, ACTH dependent Cushing' s syndrome (which includes Cushing' s disease and Ectopic ACTH Syndrome) is the most common form accounting for 60- 80 % of all cases. Cushing' s disease is caused by tumors of pituitary corticotroph cells that secrete excess ACTH. EAS is caused by tumors outside the pituitary gland that secrete excess ACTH. Cushing' s disease is an orphan indication with a prevalence of approximately 11, 000 patients in the United States. It presents more commonly in women, and usually between 30 and 50 years of age. Cushing' s disease often takes many years to diagnose and may well be under- diagnosed in the general population as many of its symptoms such as lethargy, depression, obesity, hypertension, hirsutism and menstrual irregularity can be incorrectly attributed to other more common disorders. CAH encompasses a set of disorders that..... 000 patients in the United States. EAS is a rare disorder that results from non- pituitary tumors that secrete excessive amounts of ACTH. The supraphysiological degree of ACTH secretion in EAS can vary with effects that range from cushingoid to acutely life- threatening. Treatment options for EAS are limited, with the first goal being surgical removal of the tumors, if possible. If surgery is not an option, medical therapy may be used to block cortisol production. And in some cases, adrenalectomy is required if the tumor cannot be located and medical therapy does not fully block the cortisol production. Current treatments and limitations The current treatment algorithm for CAH consists of lifelong daily glucocorticoid supplementation which attempts to address the body' s inability to synthesize cortisol as well as its over- production of androgens that results from misregulated steroidogenesis.The inability to precisely dose glucocorticoids can often lead to enduring cycles of over- or under- treatment.Under- treatment can result in adrenal crisis and intramuscular stress doses of glucocorticoid for acute illness are common.CAH patients have a two- fold risk of bone fractures compared to the general population and commonly suffer from hypercholesterolemia,insulin resistance,and hypertension.Compared to the general population,CAH patients have a diminished life expectancy of 7 years,and more than 20 % of CAH patients will die of a condition complicated by adrenal crisis.Therefore,we believe a significant unmet medical need exists for improved agents to treat both Cushing' s disease and CAH. As with acromegaly, first- line therapy for Cushing' s disease is surgery to remove the pituitary tumor if possible. Pharmacological therapy is required when surgery is delayed, contraindicated or unsuccessful. Adrenal enzyme inhibitors (e. g., metyrapone and ketoconazole) prevent the synthesis of cortisol and can improve symptoms but suffer from mechanistic side effects as a result of accumulation of precursor steroids and the resulting lack of negative feedback. For example, metyrapone is associated with hirsutism in women and patients must be monitored carefully to avoid hypoadrenalism. Ketoconazole often requires progressively increasing dosage to maintain disease control, but this is ultimately limited by the hepatotoxicity of the drug. In addition, it is a potent inhibitor of one of the most important drug metabolizing enzymes in the liver, CYP3A4, resulting in the potential for negative drug- interactions as a side effect. Mifepristone, a potent glucocorticoid receptor antagonist, is approved for control of hyperglycemia in Cushing' s syndrome, but is difficult to titrate and has significant liabilities due to its potent anti- progesterone activity. The somatostatin analog, pasireotide, inhibits ACTH secretion, but in a ~~recently~~ published study, only 15- 26 % of patients in a Phase 3 trial achieved normalization of urinary free cortisol while 73 % of patients experienced a hyperglycemia- related adverse event due to

the compound' s potent inhibition of insulin secretion. Osilodrostat, a cortisol synthesis inhibitor, received marketing approval in 2020 in the United States for the treatment of adult patients with Cushing' s disease for whom pituitary surgery is not an option or has not been curative. The current treatment algorithm for CAH consists..... Cushing' s disease and CAH. Preclinical development ACTH acts through a peptide GPCR called the melanocortin type 2 receptor, or MC2R, that is specifically expressed in the adrenal gland. Activation of MC2 by ACTH results in increased synthesis of cAMP, enhanced synthesis and secretion of cortisol and hypertrophy of adrenal cells. CRN04894 is a potent, selective nonpeptide antagonist of MC2R designed to block ACTH action and prevent its excessive stimulation of the adrenal gland in Cushing' s disease and CAH patients. In vivo proof- of- concept is demonstrated by CRN04894' s capacity to block corticosterone secretion in a rodent ACTH-challenge model, which mimics aspects of Cushing' s disease ~~. Clinical development We conducted a double- blind, randomized, placebo- controlled Phase 1 study of CRN04894 in healthy volunteers to assess the safety and tolerability of single and multiple doses of CRN04894. In addition, the study was designed to measure the effect of CRN04894 on suppression of cortisol, cortisol precursors, and adrenal androgens following exogenous ACTH stimulation. We announced positive topline data from the Phase 1 study, and CRN04894 was well tolerated and demonstrated dose- dependent increases in CRN04894 plasma concentrations. We believe CRN04894 demonstrated pharmacologic proof- of- concept, as the Phase 1 results showed reductions of both basal cortisol and elevated cortisol following an ACTH challenge. All adverse events were considered mild to moderate and there were no serious adverse events. In the fourth quarter of 2022, we entered into a Clinical Trial Agreement with the NIDDK of the NIH to collaborate on a company- sponsored multiple- ascending dose exploratory trial of CRN04894 in ADCS, including patients with Cushing's disease or EAS. This open- label study is designed to evaluate safety and pharmacokinetics of increasing doses of CRN04894 in patients with ADCS as well as to measure 24- hour urinary- free cortisol and serum cortisol as indicators of efficacy. Study activities have begun and data is expected from the study in 2024. In January 2023, we submitted an IND to the FDA for the study of CRN04894 in CAH. In February 2023, we were notified that the IND was allowed to proceed, and we have initiated study activities for a Phase 2 study in CAH patients. This open- label Phase 2 study is designed to evaluate the safety and pharmacokinetics of increasing doses of CRN04894. In addition, biomarkers, including serum androstenedione and 17 hydroxyprogesterone, will be measured as we seek to evaluate the potential efficacy of CRN04894. Data from this Phase 2 study is expected in 2024. Somatostatin receptor type 5 agonists for the treatment of hyperinsulinism We are developing CRN04777, an investigational, oral, selective nonpeptide SST5 receptor agonist that is designed to inhibit the excess insulin secretion associated with congenital and acquired disorders of hyperinsulinism, with our initial focus on congenital HI. CRN04777 is intended to act at the SST5 receptor, which is independent of many of the mutations that cause congenital HI and, therefore, should allow CRN04777 to be broadly applicable to congenital HI patients across all underlying mutations. We have completed a Phase 1 study of CRN04777 in healthy volunteers to assess the safety and tolerability of single and multiple doses of CRN04777. Following the completion of the adult healthy volunteer study under a Clinical Trial Application in Germany, in October 2022, we submitted an IND to the FDA to initiate the first U. S. clinical study of CRN04777, which is designed to evaluate the compound in a pediatric population (ages 3 months- 12 years). In November 2022, the FDA informed us that the IND was placed on clinical hold and the proposed Phase 2 clinical study may not yet be initiated. We are in the process of collecting additional information and data to submit to the FDA, with the goal of being allowed to proceed with the Phase 2 study in patients with congenital HI. The FDA has granted rare pediatric disease designation for CRN04777 for the treatment of congenital HI. In addition, the EMA has granted orphan drug designation for CRN04777 for the treatment of congenital HI and the United Kingdom MHRA has granted CRN04777 an Innovation Passport for the treatment of congenital HI. We also expect CRN04777 can be broadly developed for the treatment of other diseases characterized by excess insulin secretion, including forms of syndromic hyperinsulinism. Hyperinsulinism background Hyperinsulinism is a heterogeneous condition in which dangerously low blood sugar levels are caused by increased insulin secretion from pancreatic ß- cells. The most severe form of hyperinsulinism arises from congenital HI, a disorder whose underlying pathology is driven by genetic mutations in key genes involved in regulating insulin secretion from ß- cells. The incidence of congenital HI is approximately 1 in 30, 000 to 50, 000 new births in the United States, and it is estimated that there are 2, 200 patients in the United States, of which it is estimated that 1, 500 are eligible for pharmacotherapy because surgery was not possible or curative. Hyperinsulinism is one of the most frequent causes of persistent hypoglycemia in neonates and infants. Early diagnosis is vital to prevent neurological complications due to chronic low blood sugar, which can result in neurodevelopmental and behavior disorders, epilepsy or seizures, and even death. There are also other diseases characterized by excess insulin secretion, including forms of syndromic hyperinsulinism. Rather than being caused by a single gene mutation confined to the pancreatic beta- cell, syndromic HI may occur as part of a constellation of clinical findings in diseases where genetic mutations have pleiotropic effects outside of the beta- cell. Sotos syndrome, Beckwith Wiedemann syndrome, Kabuki syndrome and Turner' s syndrome are examples of disorders from which many patients suffer from HI. It is estimated that there are approximately 1, 700 patients with syndromic hyperinsulinisms in the United States. Hyperinsulinism can also be a severe complication for patients with insulin secreting tumors (insulinomas). Insulinomas are a specific type of NET derived from pancreatic ß- cells that secrete insulin and cause hypoglycemia. The incidence of insulinomas is 1 to 4 in 1, 000, 000 persons. Some patients who have undergone gastric bypass surgery can also present with hyperinsulinism resulting from increases in post- prandial insulin resulting in recurrent post- bariatric hypoglycemia (PBH). Maintaining glucose levels through feeding or glucose infusions is the first step in managing congenital HI. Diazoxide is the only approved therapy indicated for hyperinsulinemia. It acts at the ATP- sensitive potassium channels, or KATP, that are involved in insulin secretion and inhibits insulin secretion. However, mutations in these channels are present in approximately 55 % to 60 % of congenital HI patients, which limits the efficacy of the drug in this population. There are also serious side effects of diazoxide, which include hypertrichosis (abnormal and excessive hair growth over much of the body) and pulmonary hypertension, for which the FDA issued a warning regarding its use in infants and children. Somatostatin receptor 2 (SST2) agonists, octreotide and lanreotide, are~~

also used off- label in patients who are not adequately treated with diazoxide. Octreotide is administered as subcutaneous injections up to six times / day and can suppress both insulin and glucagon secretion. As glucagon is a primary physiologic defense mechanism against hypoglycemia, targeting SST2 is not optimal for congenital HI patients, and octreotide therapy is only used effectively in 5 % to 10 % of the patient population, and co- administration with enteral dextrose is often required. Monthly long- acting SST2 agonists, lanreotide depot and octreotide long- acting release (LAR), have replaced short- acting octreotide in some patients. Patients receiving long- acting SST2 agonists have variable glycemic profile across the month, with hyperglycemia sometimes lasting for days after the dose, and hypoglycemia often occurring prior to the next scheduled injection. Patients who fail pharmacological therapy often progress to partial or nearly complete pancreatectomy, the surgical removal of all or a part of the pancreas, which can result in type I diabetes that must be managed for the remainder of the patient' s life. We believe an orally available SST5 agonist would provide an important new therapeutic option that inhibits insulin secretion while avoiding glucagon suppression, allowing these patients to maintain normal glucose levels and possibly avoid pancreatectomy. In the process of discovering paltusotine, we synthesized many other drug- like nonpeptides, some of which also showed activity at other somatostatin receptor subtypes, including SST5. Because activation of SST5 is known to strongly inhibit insulin secretion, we focused on optimizing selective SST5 agonists to identify potential product candidates. CRN04777 was examined in a rat model of congenital HI. In this model, rats were treated with sulfonylurea glyburide, which promotes insulin release by acting at KATP channels. This activity mimics the KATP channel mutations found in about half of congenital HI patients. This high level of insulin produced a decrease of blood glucose in rats. When these rats were then treated with our development candidates, blood glucose levels returned to normal, and at higher doses, even to a hyperglycemic state. Repeat dose experiments demonstrated that insulin continued to be suppressed after seven days. Further, glucagon secretion was not suppressed in these experiments. CRN04777 met our rigorous internal criteria that we use to determine if a product candidate should enter into preclinical development. This includes extensive evaluation of pharmacology, selectivity, drug interaction potential, oral bioavailability and PK, synthetic accessibility and preliminary non- GLP safety assessments including toxicology and cardiovascular safety studies in multiple species. Additionally, preclinical safety of CRN04777 has been evaluated in in vitro and in vivo GLP studies in rats and dogs, including safety pharmacology, general toxicity, genotoxicity, and phototoxicity studies. We conducted a double- blind, randomized, placebo- controlled Phase 1 study of CRN04777 in healthy volunteers to assess the safety and tolerability of single and multiple doses of CRN04777. In addition, the study was designed to evaluate the potential mechanism of action of CRN04777 by measuring the suppression of insulin secretion in healthy volunteers following stimulation with either glucose or a sulfonylurea, agents that increase the secretion of insulin. We announced positive topline data from the single ascending dose cohorts in September 2021 and positive topline data from the multiple ascending dose cohorts in March 2022. We believe CRN04777 demonstrated pharmacologic proof- of- concept in this study, based on potent suppression of stimulated insulin observed in these subjects. The plasma exposure of CRN04777 suggested the drug was well absorbed with a half- life of approximately 40 hours, which we believe supports the potential for once daily administration in patients. All adverse events were considered mild or moderate and there were no serious adverse events. CRN04777 was well tolerated at single and multiple doses from 0. 5 mg up to 120 mg and exhibited dose- proportional pharmacokinetics for the same dose range. A dose- dependent reduction in glucose- induced insulin secretion was demonstrated with an intravenous glucose tolerance test in the SAD cohorts and a dose- dependent reversal of sulfonylurea- induced insulin secretion was seen in both the SAD and MAD cohorts. The sulfonylurea- induced insulin secretion model represents a pharmacologic analog of the hyperinsulinism that the patients experience. These data from the MAD cohorts are from 27 healthy volunteers that received daily oral doses of CRN04777 (30 mg, 60 mg or 120 mg) or placebo for 10 days with daily sampling to measure levels of fasting plasma glucose and insulin. Results showed CRN04777 treatment led to rapid, sustained and dose- dependent decreases in fasting insulin, which in turn led to dose- dependent increases in fasting plasma glucose. Pharmacokinetic and exposure profiles were consistent with expectations from the SAD cohorts. Increasing CRN04777 exposures were observed with increasing doses and the study drug was well- tolerated. On Day 10 of each of the MAD cohorts, participants underwent a challenge with a sulfonylurea, which induces HI, pharmacologically mimicking the effects of the most common genetic mutations in congenital HI. To avoid the occurrence of hypoglycemia as a result of increased insulin secretion, patients undergoing the sulfonylurea challenge were evaluated using the euglycemic clamp procedure, meaning they received intravenous (IV) glucose support, with the glucose infusion rate increasing in automated fashion to maintain safe glucose levels. One hour after the sulfonylurea challenge, the final dose of CRN04777 was administered, which led to a dose- proportional and rapid reduction of insulin secretion and glucose infusion rate requirement compared to placebo. In participants receiving 120 mg of CRN04777, the need for IV glucose support was eliminated for most patients. We are developing antagonists of the parathyroid hormone, or PTH, receptor for the treatment of primary hyperparathyroidism, or PHPT and humoral hypercalcemia of malignancy, or HHM, and other diseases of excess PTH. PTH regulates calcium and phosphate homeostasis in bone and kidney through activation of its receptor, PTHR1. Increased activation of PTHR1, either via PTH or PTH- related peptide (PTHrP, PTHLH) can lead to skeletal, renal, gastrointestinal, and neurological problems. Primary hyperparathyroidism arises from a small, benign tumor on one or more of the parathyroid glands, which results in over- secretion of PTH, leading to increased blood calcium levels, or hypercalcemia. Some patients experience no symptoms, and many can have surgery to remove the tumor and / or hyperactive gland (s), while some require management with medical therapy. Symptomatic PHPT is characterized by skeletal, renal, gastrointestinal, and neurological manifestations with increased mortality. HHM typically arises in patients with advanced- stage cancers. In cases of HHM, over- secretion of PTHrP caused by the malignant tumor results in bone resorption and calcium reabsorption in the kidney, leading to hypercalcemia. We have identified investigational, orally available nonpeptide PTH antagonists that showed activity and drug- like properties in preclinical models. We are evaluating a subset of molecules to identify potential development candidates that we believe are suitable for evaluation in human clinical trials, and we expect to select a development candidate in 2023 . Competition The commercialization of new drugs is

competitive, and we could face competition from a number of pharmaceutical or biotechnology companies around the world. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects or more convenient than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we do. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety and convenience. With respect to paltusotine, injected peptide somatostatin agonists and GH receptor antagonists are the main medical therapies for acromegaly patients where surgery is unsuccessful. There are three injected somatostatin analogs approved for the treatment of acromegaly: octreotide (marketed by Novartis AG), lanreotide (marketed by Ipsen Biopharmaceuticals, Inc.) and pasireotide (marketed by Recordati Rare Diseases Inc.). **Oral octreotide (marketed by Chiesi Farmaceutici) is approved in the U. S. for long- term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide.** Pegvisomant (marketed by Pfizer Inc.) is a daily injectable growth hormone receptor antagonist and is generally used in patients not fully controlled on somatostatin analogs. Orally administered dopamine agonists, such as bromocriptine and cabergoline, are also used. In ~~2020, Chiasma, Inc. (Chiasma acquired by Amryt Pharma, Aug 2021) received marketing approval in the United States for an oral octreotide product, MYCAPSSA, for long- term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide. In~~ December 2021, the FDA approved a lanreotide injection biosimilar manufactured by Cipla Ltd. for the treatment of acromegaly and GEP- NETs. Other products in clinical development include new formulations of peptide somatostatin agonists ~~or~~ **(Camurus AB) and** GH receptor antagonists **(** ~~. Other companies developing new pharmaceutical therapies for acromegaly include Camurus AB, Ionis Pharmaceuticals, Inc. / Antisense Therapeutics Ltd., Aquestive Therapeutics, Inc., XERIS Pharmaceuticals,~~ Amolyt Pharma **)** ~~and Rani Therapeutics, Inc~~. Injected depots of peptide somatostatin analogs are used as therapy for NETs. In adults whose carcinoid syndrome symptoms are inadequately controlled by somatostatin therapy, telotristat ethyl (marketed by TerSera Therapeutics, Inc.) is an orally administered add- on therapy. In 2018, the FDA approved Novartis' Lutathera for the treatment of somatostatin receptor **-** positive gastroenteropancreatic **NETs** ~~neuroendocrine tumors~~. Camurus, ~~Amryt~~ **Chiesi Farmaceutici** , POINT Biopharma Global Inc. **, Exelixis, RayzeBio** , and ITM Isotopen Technologien Munchen are currently engaged in Phase 3 trials of new compounds for use in the treatment of NETs and / or carcinoid syndrome symptoms. Other companies developing NETs therapeutics that target somatostatin receptors include ~~, Ipsen,~~ Oranomed / RadioMedix, ~~Xencor, Tarveda Therapeutics, Advanced Accelerator Applications SA,~~ ASCIL Biopharm ~~, DexTech Medical, Aquestive Therapeutics Inc.~~, Molecular Targeting Technologies Inc., **Perspective Therapeutics** ~~Viewpoint Molecular Targeting LLC, Xeris Pharmaceuticals~~ , and Immunwork Inc ~~. With respect to congenital HI, maintaining glucose levels through feeding or glucose infusions is the first step in managing the disease. Diazoxide (marketed by Teva Pharmaceuticals, Inc.) is the only approved therapy indicated for hyperinsulinemia. Octreotide (used off- label) is administered as subcutaneous injections in those who respond poorly to diazoxide. Patients who fail pharmacological therapy often progress to partial or nearly complete pancreatectomy, which can result in type I diabetes that must be managed for the remainder of the patient' s life. Ready- to- use glucagon analog products have also been approved and could be used to treat congenital HI if a patient experiences severe hypoglycemia and includes Zegalogue, which received approval in 2021 and is marketed by Zealand Pharma A / S, and Gvoke HypoPen, which received approval in 2019 and is marketed by Xeris Pharmaceuticals, Inc,. Companies developing products for potential use in congenital HI include Rezolute, Inc., Hanmi Pharmaceuticals, Eiger Biopharmaceuticals, Inc., Sosei Heptares and AmideBio~~ . As with acromegaly, first- line therapy for Cushing' s disease is surgery to remove the pituitary tumor if possible. ~~Use~~ **The use** of adrenal enzyme inhibitors (metyrapone, ketoconazole and more recently levoketoconazole which gained FDA approval in December 2021 and is marketed by Xeris Pharmaceuticals) prevent the synthesis of cortisol and can improve symptoms. Mifepristone (marketed by Corcept Therapeutics, Inc.), a glucocorticoid receptor antagonist, is approved for control of hyperglycemia in **Cushing' s syndrome. A generic form of mifepristone has been approved for the treatment of endogenous** Cushing' s syndrome. Osilodrostat (marketed by Recordati), a cortisol synthesis inhibitor, is approved for the treatment of endogenous Cushing' s syndrome. The somatostatin agonist pasireotide is also approved for Cushing' s disease. Other companies developing products for potential use in Cushing' s disease include Corcept Therapeutics, Inc., **Sparrow Pharmaceuticals,** and Cyclacel Pharmaceuticals, Inc. Neurocrine Biosciences and Spruce Biosciences are developing CRF receptor antagonists for the treatment of CAH. BridgeBio Pharma is also developing a potentially curative gene therapy treatment for CAH targeting the 21- hydroxylase enzyme. There may be other earlier **-** stage clinical programs that, if approved, would compete with our products. Many of our competitors have substantially greater financial, technical and human resources than we have. Additional mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated ~~in~~ **on** our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields. Our success will be based in part on our ability to build and actively manage a portfolio of drugs that ~~addresses~~ -- **address** unmet medical needs and ~~creates~~ - **create** value in patient therapy. Intellectual property We actively protect our commercially important proprietary technology by, among other methods, obtaining, maintaining, and defending our patent rights. Issued patents can provide protection for varying periods of time, depending upon the date of filing of the patent application, the date of patent issuance and the legal term of patents in the countries in which they are obtained. In general, patents issued for applications filed in the United States can provide exclusionary rights for 20 years from the earliest effective non- provisional filing date. In addition, in certain instances, the term of an issued U. S. patent that covers or claims an FDA approved product can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period, which is called patent term extension. The period of patent term extension in the United States cannot be longer than five years and the total patent term, including the extension period, must not exceed 14 years following FDA approval. The term of patents outside of the United States varies in accordance with the laws of the foreign jurisdiction, but typically is also 20 years from the earliest effective non- provisional filing date.

However, the actual protection afforded by a patent varies on a product- by- product basis, from country- to- country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory- related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. Some countries also provide mechanisms to recapture a portion of the patent term lost during regulatory review, similar to patent term extension in the United States. The amount of patent term that can be recaptured depends on the laws of the relevant jurisdictions. There is no guarantee that the applicable authorities, including the USPTO in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions. For more information regarding the risks related to our intellectual property, see " Risk Factors- Risks Related to Our Intellectual Property. " We have filed numerous patent applications covering our internally developed product candidates in the United States and in jurisdictions outside of the United States, resulting in multiple issued patents. We ~~currently~~ file patent applications **geographically broadly** ~~covering the compounds in our lead product candidates in the United States~~ , ~~Europe, Japan, China, South Korea, Australia, Canada, Israel, Mexico, Taiwan, Brazil, India, Eurasia, New Zealand, Ukraine, Indonesia, Singapore, and South Africa, and certain candidates~~ in **multiple pharmaceutical markets** ~~Hong Kong, Malaysia, Philippines, Thailand, Vietnam, Chile, Colombia, Argentina, Peru, Venezuela,~~ and ~~Egypt~~ **in alignment with our commercial strategy** . We pursue patent protection for all inventions and improvements throughout development, including, when possible, compositions of matter, methods of use, dosage regimens, formulations, crystalline forms (polymorphs), and manufacturing processes. We own multiple issued patents and pending patent applications relating to our lead product candidate paltusotine. Issued patents claiming the compound paltusotine as composition- of- matter have been obtained in the United States, Europe, China, and Japan, among other jurisdictions, and are estimated to expire in 2037, not including any available patent term adjustments or extensions. We own additional issued patents and pending patent applications relating to our lead product candidate paltusotine, its methods of use, dosage regimens, formulations, and crystalline forms (polymorphs), which, when issued, are estimated to expire between 2039 and ~~2043~~ **2044** , not including any available patent term adjustments or extensions. We own multiple issued patents and pending patent applications relating to our ACTH antagonist product candidate CRN04894. Issued patents claiming the compound CRN04894 as composition- of- matter have been obtained in the United States and **Japan, among other jurisdictions, and** are estimated to expire in 2039, not including any available patent term adjustments or extensions. We own additional pending patent applications relating to our ~~lead~~ product candidate CRN04894, its methods of use, and crystalline forms (polymorphs), which, when issued, are estimated to expire between 2042 and ~~2043~~ **2044** , not including any available patent term adjustments or extensions. We own ~~an~~ **a variety of other** issued ~~patent~~ **patents** and ~~multiple~~ pending patent applications ~~relating~~ **related** to ~~our SST5 product candidate CRN04777~~ **various compounds, pharmaceutical compositions and methods of use** . ~~An~~ **The** issued **patents, and any patents that may issue from the pending** patent **applications, are** ~~claiming the compound CRN04777 as composition- of- matter has been obtained in the United States and is~~ estimated to expire ~~in~~ **between 2036 and** ~~2040~~ **2044** , not including any available patent term adjustments or extensions. We ~~own additional patent applications relating to our lead product candidate CRN04777, its methods of use, and crystalline forms (polymorphs), which, when issued, are estimated to expire in 2042, not including any available patent term adjustments or extensions. We own a variety of other issued patents and pending patent applications related to various compounds, pharmaceutical compositions and methods of use. The issued patents, and any patents that may issue from the pending patent applications, are estimated to expire between 2036 and 2043, not including any available patent term adjustments or extensions. We~~ also possess substantial know- how and trade secrets relating to the development and commercialization of our product candidates, including related manufacturing processes and technology, which strengthen and maintain our proprietary position in the field of endocrinology. We own ~~one~~ registered ~~trademark~~ **trademarks and have pending registration applications protecting our corporate marks** in the United States ~~;~~ **and in jurisdictions outside of** ~~three~~ **the United States** ~~registered trademarks in the UK , and three registered trademarks~~ in ~~the European Union~~ **multiple pharmaceutical markets and in alignment with our commercial strategy** . We also plan to rely on data exclusivities and market exclusivities, when available, to provide additional protection for our products. Certain intellectual property rights, including for our lead programs, have been generated through the use of U. S. government funding provided from our Small Business Innovation Research Grants, or SBIR Grants, awarded to us by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, and are therefore subject to certain federal regulations. As a result, the U. S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh- Dole Act of 1980. Manufacturing Manufacturing, testing and storage of our product candidates for nonclinical and clinical studies is conducted at third- party contract manufacturers and distributors. We do not plan to build plants or facilities for development or commercial scale manufacture or storage of our product candidates. To date, the contract manufacturers have met our manufacturing requirements, and we expect them to be capable of providing sufficient quantities of our product candidates to meet estimated full- scale commercial needs. However, the contract manufacturers may be required to increase production scale, or we may need to secure alternate suppliers. Commercialization We ~~intend~~ **have started** to build the infrastructure to effectively support the commercialization of our product candidates, **in anticipation of** if and when ~~we believe a~~ regulatory approval of the first of such product candidates in a particular geographic market appears imminent. The infrastructure for orphan products typically consists of medical liaisons and a targeted, specialty sales force that calls on a focused group of physicians supported by sales management, internal sales support, an internal marketing group and distribution support. One challenge unique to commercializing therapies for rare diseases is the difficulty in identifying eligible patients due to the very small and sometimes heterogeneous disease populations. Additional capabilities important to the orphan marketplace include the management of key accounts, such as managed care organizations, group purchasing organizations, specialty pharmacies and government accounts. To develop the appropriate commercial infrastructure, we **have invested and** will ~~have~~ **continue** to invest significant amounts of financial and management resources, some of which **has been and** will **continue to** be committed prior to any confirmation that any of our product candidates will be approved. Where appropriate, we

may elect in the future to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our product candidates **, such as the Sanwa License and the Loyal License** . In certain instances, we may consider building our own commercial infrastructure. **U. S.** Government ~~regulation~~ **Regulation** Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record- keeping, promotion, advertising, distribution, marketing and export and import of products such as those we are developing. A new drug must be approved by the FDA through the ~~New Drug Application, or~~ NDA ~~,~~ process before it may be legally marketed in the United States **. The process of complying with the extensive regulations and obtaining these approvals and, if approved, the subsequent compliance with applicable federal, state and local statutes and regulations require the expenditure of substantial management and financial resources. Our business is subject to extensive regulation in the U. S., including the FDA as noted above, and by foreign regulatory authorities, including the EMA. We are required in the U. S. and in the other regions and countries we may intend to commercialize our drug products to obtain approval from regulatory authorities before we manufacture, market and sell our products. If our products obtain regulatory approval, they are subject to U. S. and ex-U. S. regulatory agency authority which may require additional testing and reporting, inspections, or changes to product labeling** . U. S. drug development process In the United States, the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act, or the FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U. S. requirements at any time during the product development process, approval process or after approval may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA' s refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us. The process required by the FDA before a drug may be marketed in the United States generally involves the following: • completion of preclinical laboratory tests, animal studies and formulation studies in accordance with GLP regulations and other applicable regulations; • submission to the FDA of an IND, which must become effective before human clinical trials may begin; • approval by an independent institutional review board, or IRB, or ethics committee at each clinical site before each trial may be initiated; • performance of adequate and well- controlled human clinical trials in accordance with good clinical practice, or GCP, regulations to establish the safety and efficacy of the proposed drug for its intended use; • submission to the FDA of an NDA after completion of all pivotal trials; • satisfactory completion of an FDA advisory committee review, if applicable; • satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current Good Manufacturing Practice, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug' s identity, strength, quality and purity, and of selected clinical investigation sites to assess compliance with GCP; and • FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the United States. Once a product candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. An IND will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated, if the trial includes an efficacy evaluation. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30- day time period, places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during clinical trials due to safety concerns about on- going or proposed clinical trials or non- compliance with specific FDA requirements, and the trials may not begin or continue until the FDA notifies the sponsor that the hold has been lifted. All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP regulations, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials must be conducted under protocols detailing the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and a separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. While the IND is active, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report, among other information, must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the same or similar drugs, findings from animal or in vitro testing suggesting a significant risk to humans, and any clinically important increased incidence of a serious suspected adverse reaction compared to that listed in the protocol or investigator brochure. Furthermore, an independent IRB at each institution participating in the clinical trial must review and approve each protocol before a clinical trial commences at that institution and must also approve the information regarding the trial and the consent form that must be provided to each trial subject or his or her legal representative, monitor the study until completed and otherwise comply with IRB regulations. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB' s requirements or if the drug has been associated with unexpected

serious harm to patients. In addition, some clinical trials are overseen by an independent group of qualified experts organized by the sponsor, known as a data safety monitoring board or committee. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries, including clinicaltrials. gov. Human clinical trials are typically conducted in three sequential phases that may overlap or be combined: • Phase 1: The product candidate is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early indication of its effectiveness. In the case of some products for severe or life- threatening diseases, such as cancer, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients. • Phase 2: The product candidate is administered to a limited patient population with a specified disease or condition to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance and appropriate dosage. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials. • Phase 3: The product candidate is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk- benefit ratio of the product candidate and provide an adequate basis for product labeling. Post- approval trials, sometimes referred to as Phase 4 studies, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA. During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the end of Phase 2, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and the FDA to reach agreement on the next phase of development. Sponsors typically use the meetings at the end of the Phase 2 trial to discuss Phase 2 clinical results and present plans for the pivotal Phase 3 clinical trials that they believe will support approval of the new drug. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug. In addition, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life. U. S. review and approval process The results of product development, preclinical and other non- clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once filed, the FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP- compliant to assure and preserve the product' s identity, strength, quality and purity. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of " filing " of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a " filing " decision after it the application is submitted. The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured. Additionally, before approving an NDA, the FDA may inspect one or more clinical trial sites to assure compliance with GCP requirements. After the FDA evaluates an NDA and conducts inspections of manufacturing facilities where the investigational product and / or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter, or CRL. An approval letter authorizes commercial marketing of the drug with prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL usually describes the specific deficiencies in the NDA identified by the FDA and may require additional clinical data, such as an additional clinical trial or other significant and time- consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a CRL is issued, the sponsor must resubmit the NDA or, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval. If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. In addition, the FDA may require a sponsor to conduct Phase 4 testing, which involves clinical trials designed to further assess a drug' s safety and effectiveness after NDA approval, and may require testing and surveillance programs to monitor the safety of approved products which have been commercialized. The FDA may also place other conditions on approval including the requirement for a risk evaluation and mitigation strategy, or

REMS, to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. In addition, the Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric clinical trials for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs and supplements must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must evaluate the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric clinical trials for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug is ready for approval for use in adults before pediatric clinical trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric clinical trials begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation. Orphan drug designation Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200, 000 individuals in the United States or, if it affects more than 200, 000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or inability to manufacture the product in sufficient quantities. The designation of such drug also entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user- fee waivers. However, competitors, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan exclusivity also could block the approval of a competing product for seven years if a competitor obtains approval of the same drug as defined by the FDA or if a product candidate is determined to be contained within the competitor' s product for the same disease or condition. In addition, if an orphan designated product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan exclusivity. Expedited development and review programs The FDA has a fast track designation program that is intended to expedite or facilitate the process for reviewing new drug products that meet certain criteria. Specifically, new drugs are eligible for fast track designation if they are intended to treat a serious or life- threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. The sponsor of a fast track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and, once an NDA is submitted, the product candidate may be eligible for priority review. With regard to a fast track product candidate, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. A product candidate intended to treat a serious or life- threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product candidate can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers. Any product candidate submitted to the FDA for approval, including a product candidate with a fast track designation or breakthrough designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. An NDA is eligible for priority review if the product candidate is designed to treat a serious condition, and if approved, would provide a significant improvement in safety or efficacy compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review. The FDA endeavors to review applications with priority review designations within six months of the filing date as compared to ten months for review of new molecular entity NDAs under its current PDUFA review goals. In addition, a product candidate may be eligible for accelerated approval. Drug products intended to treat serious or life- threatening diseases or conditions may be eligible for accelerated approval upon a determination that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA generally requires that a sponsor of a drug receiving accelerated approval perform adequate and well- controlled confirmatory clinical trials. Drugs receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required

confirmatory trials in a timely manner or if such trials fail to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre- approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast track designation, priority review and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Post- approval requirements Any products manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record- keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications, certain manufacturing changes and additional labeling claims, are subject to further FDA review and approval. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP regulations and other laws and regulations. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance. The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post- market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things: • restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls; • fines, warning letters, or untitled letters; • clinical holds on clinical studies; • refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals; • product seizure or detention, or refusal to permit the import or export of products; • consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs; • mandated modification of promotional materials and labeling and the issuance of corrective information; • the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or • injunctions or the imposition of civil or criminal penalties. In addition, the FDA closely regulates the marketing, labeling, advertising and promotion of drug products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product' s labeling and that differ from those tested by us and approved by the FDA. Such off- label uses are common across medical specialties. Physicians may believe that such off- label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer' s communications on the subject of off- label use of their products. Marketing exclusivity Market exclusivity provisions under the FDCA can delay the submission or the approval of certain marketing applications. The FDCA provides a five- year period of non- patent data exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not approve or even accept for review an abbreviated new drug application, or ANDA, or an NDA submitted under Section 505 (b) (2), or 505 (b) (2) NDA, submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovative drug or for another indication, where the applicant does not own or have a legal right of reference to all of the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non- infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA alternatively provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three- year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs or 505 (b) (2) NDAs for drugs containing the active agent for the original indication or condition of use. Five- year and three- year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well- controlled clinical trials necessary to demonstrate safety and effectiveness. Pediatric exclusivity is another type of marketing exclusivity available in the United States. Pediatric exclusivity provides for an additional six months of marketing exclusivity attached to another period of exclusivity if a sponsor conducts clinical trials in children in response to a written request from the FDA. The issuance of a written request does not require the sponsor to undertake the described clinical trials. U. S. coverage and reimbursement Significant uncertainty exists as to the coverage and reimbursement status of any therapeutic product candidate for which we may seek regulatory approval. Sales in the United States will depend in part on the availability of sufficient coverage and adequate reimbursement from third- party payors, which include government health programs such as Medicare, Medicaid, TRICARE and the Veterans Administration, as well as managed care organizations and private health

insurers. Prices at which we or our customers seek reimbursement for our therapeutic product candidates can be subject to challenge, reduction or denial by payors. The process for determining whether a payor will provide coverage for a product is typically separate from the process for setting the reimbursement rate that the payor will pay for the product. A payor' s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be available. Additionally, in the United States there is no uniform policy among payors for coverage or reimbursement. Third- party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies, but also have their own methods and approval processes. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. If coverage and adequate reimbursement are not available, or are available only at limited levels, successful commercialization of, and obtaining a satisfactory financial return on, any product we develop may not be possible. Third- party payors are increasingly challenging the price and examining the medical necessity and cost- effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for marketing, we may need to conduct expensive studies in order to demonstrate the medical necessity and cost- effectiveness of any products, which would be in addition to the costs expended to obtain regulatory approvals. Third- party payors may not consider our product candidates to be medically necessary or cost- effective compared to other available therapies, or the rebate percentages required to secure favorable coverage may not yield an adequate margin over cost or may not enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Healthcare reform In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of drug product candidates, restrict or regulate post- approval activities, and affect the profitable sale of drug product candidates. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and / or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives ~~. In March~~ **, including the** 2010 ~~, the~~ Patient Protection and Affordable Care Act, as subsequently ~~amended by as~~ amended by the Health Care and Education Reconciliation Act, collectively the ACA, was passed, which substantially changed the way healthcare is financed by both the government and private insurers, and significantly impacts the U. S. pharmaceutical industry. The ACA, as amended, among other things: (1) increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations; (2) established an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs; (3) expanded the availability of lower pricing under the 340B drug pricing program by adding new entities to the program; (4) increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program; (5) expanded the eligibility criteria for Medicaid programs; (6) created a new Patient- Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; (7) created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70 % point- of- sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer' s outpatient drugs to be covered under Medicare Part D; **and** (8 ~~)~~ ~~established a new Patient- Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and (9~~) established a Center for Medicare and Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drugs. Since its enactment, there have been judicial, Congressional and executive challenges to certain aspects of the ACA. On June 17, 2021, the U. S. Supreme Court dismissed the most recent judicial challenge to the ACA without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court' s decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers, which was temporarily suspended from May 1, 2020 through March 31, 2022. In addition, on March 11, 2021, the American Rescue Plan Act of 2021 was signed into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100 % of a drug' s average manufacturer price, or AMP, beginning January 1, 2024. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. ~~On~~ **In addition, on** August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical 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, designed to encourage importation from other countries and bulk purchasing. U. S. healthcare fraud and abuse laws and compliance requirements Federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws include anti- kickback and false claims laws and regulations, and transparency laws and regulations with respect to drug pricing and payments or other transfers of value made to physicians and other licensed healthcare professionals. The federal Anti- Kickback Statute prohibits, among other things, individuals or entities from knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. The federal civil and criminal false claims laws, including the civil False Claims Act, prohibit, among other things, any individual or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal civil and criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program. Similar to the federal Anti- Kickback Statute, a person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program, with specific exceptions, to report annually to CMS information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non- physician practitioners including physician assistants and nurse practitioners, and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members. Similar state and foreign laws and regulations may also restrict business practices in the biopharmaceutical industry, such as state anti- kickback and false claims laws, which may apply to business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers, or by patients themselves; state laws that require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to physicians, other healthcare providers and entities; state and local laws that require the registration of pharmaceutical sales representatives. Efforts to ensure compliance with applicable healthcare laws and regulations can involve substantial costs. Violations of healthcare laws can result in significant penalties, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, individual imprisonment, possible exclusion from participation in Medicare, Medicaid and other U. S. healthcare programs, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of operations. Data Privacy and Security Numerous state, federal and foreign laws, including consumer protection laws and regulations, govern the collection, dissemination, use, access to, confidentiality and security of personal information, including health- related information. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy laws, and consumer protection laws and regulations (e. g., Section 5 of the FTC Act), that govern the collection, use, disclosure, and protection of health- related and other personal information could apply to our operations or the operations of our partners. **For example, California enacted the California Consumer Privacy Act, or CCPA, effective January 1, 2020, which gives California residents expanded rights to access, correct, and delete their personal information, opt out of certain personal information sharing and disclosure, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risks associated with, data breach litigation. The CCPA may increase our compliance costs and potential liability. Further, the California Privacy Rights Act, or CPRA, generally went into effect on January 1, 2023, and significantly amends the CCPA. The CPRA imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement, and additional compliance investment and potential business process changes may be required. Similar laws have passed or been proposed in other states and at the federal level.** In addition, certain foreign laws govern the privacy and security of personal data, including health- related data. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and / or criminal penalties and restrictions on data processing. **See " Risk Factors – Risks related to our business operations and industry " for additional information about the risks to our business associated with a breach or compromise to our information technology systems.** Cybersecurity In the normal course of business, we may collect and store personal information and certain sensitive company information, including proprietary and confidential business information, trade secrets, intellectual property, information regarding trial participants in connection with clinical trials, sensitive third- party information and employee

information. To protect this information, **we** ~~our existing cybersecurity policies require monitoring and detection programs, network security measures, encryption of critical data, and security assessment of vendors. We maintain various protections designed to safeguard against cyberattacks, including firewalls and virus detection software. We~~ have **implemented a** ~~established and test our disaster recovery plan and we protect against business interruption by backing up our major systems. In addition, we periodically scan our environment for any vulnerabilities, perform penetration testing and engage third parties to assess effectiveness of our data security practices. A third party security consultant conducts regular network security reviews, scans and audits. In addition, we maintain insurance that includes cybersecurity coverage. Despite the implementation of our~~ cybersecurity program **, described under Item 1C, " Cybersecurity " below. Nonetheless** , our security measures cannot guarantee that a significant cyberattack will not occur. A successful attack on our information technology systems could have significant consequences to the business ~~. While we devote resources to our security measures to protect our systems and information, these measures cannot provide absolute security~~ . See " Risk Factors – General Risk Factors " for additional information about the risks to our business associated with a breach or compromise to our information technology systems. Employees and Human Capital Resources As of February ~~24~~ **20** , ~~2023~~ **2024** , we had ~~210~~ **290** full- time employees, ~~55~~ **77** of whom have a Ph. D. or M. D. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good. In addition, we rely on a number of consultants to assist us. Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integration our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock- based compensation awards and cash-based performance bonus awards, in order to increase stockholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives. We maintain limited product liability insurance coverage for our clinical trials in the amount of $ 10 million per occurrence and $ 10 million in the aggregate. However, insurance coverage is becoming increasingly expensive, and we may not be able to obtain or maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. About Crinetics We were formed as a Delaware corporation on November 18, 2008. **In January 2017, we formed a wholly- owned Australian subsidiary, Crinetics Australia Pty Ltd, or CAPL, to conduct various preclinical and clinical activities for our product and development candidates in Australia. In December 2023, we moved our corporate headquarters to a new facility which consists of a 94, 230 square foot leased laboratory and office space in San Diego, California.** Our **previous headquarters consisted of a 29, 499 square foot leased facility in San Diego, California. Our current** principal executive offices are located at **6055 Lusk** ~~10222 Barnes Canyon Road, Bldg~~ **Blvd** ~~# 2,~~ San Diego, ~~California~~ **CA** 92121, and our telephone number is (858) 450- 6464 ~~. In January 2017, we formed a wholly- owned Australian subsidiary, Crinetics Australia Pty Ltd, or CAPL, to conduct various preclinical and clinical activities for our product and development candidates in Australia~~ . Available Information Our Annual Reports on Form 10- K, Quarterly Reports on Form 10- Q, Current Reports on Form 8- K and amendments to reports filed pursuant to Sections 13 (a) and 15 (d) of the Exchange Act are available free of charge on our website at www. crinetics. com, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. The address of that website is www. sec. gov. We use our investor relations website as a means of disclosing material non- public information and for complying with our disclosure obligations under Regulation FD. Investors should monitor such website, in addition to following our press releases, SEC filings and public conference calls and webcasts. Information relating to our corporate governance is also included on our investor relations website. The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this filing. Further, our references to the URLs for these websites are intended to be inactive textual references only. Item 1A. Risk Factors Investing in our **securities** ~~common stock~~ involves a high degree of risk. You should consider carefully the risks and uncertainties described below, together with all of the other information included in this Annual Report on Form 10- K, including our consolidated financial statements and **the** related notes **thereto** and " Management' s Discussion and Analysis of Financial Condition and Results of Operations, " before making an investment decision to purchase or sell ~~shares of~~ our **securities** ~~common stock~~ . If any of the following risks are realized, our business, financial condition, results of operations and prospects could be materially and adversely affected. In that event, the trading price of our **securities** ~~common stock~~ could decline, and you could lose part or all of your investment. The risks described below are not the only ones that we may face, and additional risks or uncertainties not known to us or that we currently deem immaterial may also impair our business and future prospects. Risks related to our limited operating history, financial position and capital requirements Pharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We are a clinical- stage pharmaceutical company with a limited operating history upon which you can evaluate our business and prospects. We commenced operations in 2010 ~~,~~ and **,** to date, we have focused primarily on organizing and staffing our company, business planning, raising capital, discovering potential product candidates, and conducting preclinical studies and clinical trials. Our approach to the discovery and development of product candidates is unproven, and we do not know whether we will be able to develop any products of commercial value. In addition, only ~~three~~ **two** of our product candidates, paltusotine ~~, CRN04777,~~ and CRN04894 are in clinical development, while our other development programs remain in the preclinical or discovery stages. We have not yet demonstrated an ability to successfully ~~complete any pivotal clinical trials beyond Phase 2,~~ obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products. We **are not profitable and** have incurred significant operating losses since our inception. If our product candidates are not successfully developed and approved, we may never generate any revenue **from commercial sales.**

In addition, our product candidates, even if successfully developed and approved, may not achieve commercial success . We have incurred cumulative net losses since our inception and, as of December 31, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~439~~ **653** . ~~2~~ **7** million. Our losses have primarily resulted from expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations. All of our product candidates will require substantial additional development time and resources before we would be able to apply for or receive regulatory approvals and begin generating revenue from product sales. We expect to continue to incur losses for the foreseeable future, and we anticipate these losses will increase substantially as we continue our development of, seek regulatory approval for and potentially commercialize any approved products. To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. In addition, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical industry. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product candidates or even continue our operations **, any** ~~. A decline in the value~~ of **which** ~~our company~~ could ~~also cause you~~ **materially and adversely affect our business, prospects, results of operations and the trading price of our common stock. We will require substantial additional financing** to ~~lose~~ **achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at** all **, could lead us to delay, limit, reduce, abandon,** or **terminate** ~~part of your~~ **our** ~~investment~~ **product development programs, commercialization efforts or other operations** . The development of biopharmaceutical product candidates ~~is~~ **and conducting preclinical studies and clinical trials are time- consuming and** capital- intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct our ongoing and planned clinical trials of paltusotine ~~,~~ ~~CRN04777,~~ and CRN04894 ~~and~~ **,** continue our research and development activities ~~and~~ **,** conduct preclinical studies for our other development programs, and seek regulatory approval for our current product candidates and any future product candidates, including product candidates that we may develop for **hyperparathyroidism,** polycystic kidney disease, metabolic diseases (including diabetes and obesity) and Graves' Disease (including **TED** ~~Thyroid Eye Disease~~), among other indications. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. ~~Because the outcome of any preclinical study or clinical trial is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates.~~ Furthermore, we incur, and expect to continue to incur, additional costs associated with operating as a public company. **At the same time, our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all.** Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, ~~we~~ **it** could ~~be forced~~ **lead us** to delay, **limit,** reduce ~~or eliminate~~ **, abandon** ~~our~~ **or terminate some or all of our product candidates,** research and development programs ~~or~~ **,** any future commercialization efforts **, or other operations** . We believe that our existing cash, cash equivalents and investment securities will enable us to fund our operations for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our operating plans and other demands on our cash resources may change as a result of many factors currently unknown to us **. Because the outcome of any preclinical study or clinical trial is highly uncertain** , **we cannot reasonably estimate the actual amounts necessary to successfully complete the development** and **commercialization of our product candidates.Our future capital requirements will depend on many factors,including:• the type,number,scope,progress,expansions,results,costs and timing of our preclinical studies and clinical trials of our product candidates which we are pursuing or may choose to pursue in the future;• the costs and timing of manufacturing and laboratory testing for our product candidates,including clinical supplies and commercial manufacturing if any product candidate is approved;• the costs,timing and outcome of regulatory review of our product candidates;• the costs of obtaining,maintaining and enforcing our patents and other intellectual property rights;• our efforts to enhance operational** systems and hire additional personnel to satisfy our obligations as a public company,including enhanced internal controls over financial reporting;• the costs associated with hiring additional **and retaining existing** personnel and consultants as our preclinical and clinical activities increase;• the timing and the extent of any Australian Tax Incentive refunds and future grant revenues,if any,that we receive;• the costs and timing of establishing or securing sales and marketing capabilities if any product candidate is approved;• our ability to achieve sufficient market acceptance,adequate coverage and reimbursement from third- party payors and adequate market share and revenue for any approved products **;• the effect of competing technological and market developments** ;• the terms and timing of establishing and maintaining collaborations,licenses and other similar arrangements;• our ability to receive sales- based milestones under our collaboration and license agreements and other potential future similar arrangements;• costs associated with any products or technologies that we may in- license or acquire;• the funding of any co- development arrangements we enter into;and • our ability to participate in **any** future equity offering by Radionetics ~~,including our option to exercise our warrant for the purchase of Radionetics stock.Identifying potential product candidates and conducting preclinical studies and clinical trials is a time-~~

~~consuming,expensive and uncertain process that takes years to complete,and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales.In addition,our product candidates,if approved,may not achieve commercial success.Our commercial revenues,if any,will be derived from sales of products that we do not expect to be commercially available for many years,if at all~~ .Accordingly, ~~we will need to continue to rely on additional financing to achieve our business objectives.Adequate additional financing may not be available to us on acceptable terms,or at~~ we may need to seek additional funds sooner than planned, **including** through public or private equity or debt financings ~~, such as our follow- on public offerings and private placements completed in 2021 and 2022,~~ or other sources ~~, including~~ **or through** strategic collaborations **. In August 2019 we entered into a Sales Agreement, or the Sales Agreement, with SVB Leerink LLC and Cantor Fitzgerald & Co., or the Sales Agents, under which we have and may, from time to time, sell up to $ 150. 0 million of shares of our common stock through the Sales Agents. However, there can be no assurance that the Sales Agents will be successful in consummating future sales based on prevailing market conditions or in the quantities or at the prices that we deem appropriate. In addition, the Sales Agreement may be terminated by us or the Sales Agents at any time upon ten days' notice to the other parties, or by either Sales Agent, with respect to itself, at any time in certain circumstances, including the occurrence of a material adverse change. Attempting to secure additional financing may divert our management from our day- to- day activities, which may adversely affect our ability to develop our product candidates. Adequate additional financing may not be available to us on acceptable terms, or at all** . We do not currently have any active grants nor do we expect grant revenues to be a material source of future revenue. **If** ~~In addition,~~ we **are unable** ~~may seek additional capital due~~ to **obtain funding on a timely basis,** ~~favorable market conditions or strategic considerations even if~~ we ~~believe we have sufficient funds~~ **may be required to significantly curtail, delay** ~~for~~ **or discontinue one** ~~our~~ **or** ~~current~~ **more of** ~~or~~ **our research or development programs, including our clinical trial programs, or any** future **commercialization** ~~operating plans. For example, in August 2019 we entered into a Sales Agreement, or the Sales Agreement, with SVB Leerink LLC and Cantor Fitzgerald & Co., or the Sales Agents, under which we may, from time to time, sell up to $ 150. 0 million~~ of ~~shares of our common stock through the Sales Agents. However, there can be no assurance that the Sales Agents will be successful in consummating future sales based on prevailing market conditions or in the quantities or at the prices that we deem appropriate. In addition, the Sales Agreement may be terminated by us or the Sales Agents at~~ any ~~time upon ten days' notice to the other parties, or by either Sales Agent, with respect to itself, at any time in certain circumstances, including the occurrence of a material adverse change. Attempting to secure additional financing may divert our management from our day- to- day activities, which may adversely affect our ability to develop our~~ product candidates ~~. Our future~~ **, or be unable to sustain or expand our operations or otherwise** ~~capital~~ **capitalize** ~~requirements will depend~~ on **our business opportunities, as desired,** ~~many~~ **any** ~~factors~~ **of which could materially affect our business** , **financial condition and** ~~including: • the type, number, scope, progress, expansions,~~ results ~~, costs and timing~~ of ~~, our preclinical studies and clinical trials of our product candidates which we are pursuing or may choose to pursue in the future; • the costs and timing of manufacturing for our product candidates, including commercial manufacturing if any product candidate is approved; • the costs, timing and outcome of regulatory review of our product candidates; • the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights; • our efforts to enhance operational~~ **operations** systems and hire additional personnel to satisfy..... reduce the value of our common stock . Risks related to the discovery and development and regulatory approval of our product candidates We are in the early stages of our development efforts and have only ~~three~~ **two** product candidates, paltusotine ~~, CRN04777,~~ and CRN04894, in clinical development. All of our other development programs are still in the preclinical or drug discovery stage. We have invested substantially all of our efforts and financial resources in developing our current product candidates, potential product candidates and conducting preclinical studies and clinical trials. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the **factors discussed elsewhere in this " Risk Factors " section, and on the completion of each of the** following: • completion of preclinical studies and clinical trials with favorable results; • acceptance of INDs by the FDA or acceptance of similar regulatory filing by comparable foreign regulatory authorities for the conduct of clinical trials of our product candidates and our proposed design of future clinical trials; • receipt of marketing approvals from applicable regulatory authorities, including NDAs ~~,~~ from the FDA **,** and maintaining such approvals; • making arrangements with our third- party manufacturers for, or establishing, commercial manufacturing capabilities; • maintaining an acceptable safety profile of our products following approval; and • maintaining and growing an organization of scientists and businesspeople who can develop our products and technology. The success of our business, including our ability to finance our company and generate any revenue in the future, will primarily depend on the successful development, regulatory approval and commercialization of paltusotine, as well as our other product candidates, which may never occur. In the future, we may also become dependent on other product candidates that we may develop or acquire ~~; however, given our current stage of development, it may be several years, if at all, before we have demonstrated the safety and efficacy of a treatment sufficient to warrant approval for commercialization~~ . If we are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize our product candidates, **our business will be materially adversely affected, and** we may not be able to generate sufficient revenue to continue our business. The success of our business depends primarily upon our ability to discover, develop, and commercialize products created with our internal capabilities, including the experience of our scientists and drug development staff **. We intend to expand our existing pipeline of core assets by advancing product candidates from current ongoing discovery programs into clinical development. However, research programs to identify product candidates are expensive, time- consuming and unpredictable, and can require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified** . While we believe we have a highly productive drug discovery and development organization, we ~~have not yet succeeded and may not succeed in demonstrating efficacy and safety for any product candidates in~~

~~clinical trials or in obtaining marketing approval thereafter. We~~ may be unsuccessful in discovering additional product candidates, moving such product candidates from preclinical studies into clinical development ~~,~~**. Although our product candidates all target endocrine diseases** and **endocrine- related tumors, we cannot assure you that any additional preclinical programs will be able to progress from candidate identification to Phase 1 clinical proof- of- concept in healthy volunteers. Moreover,** any product candidates that we ~~are currently~~ **recommend for clinical** ~~developing~~ **development** may be shown to have harmful side effects or may have other characteristics that may necessitate additional clinical testing or make the product candidates unmarketable or unlikely to receive marketing approval. If any of these events occur, we may **choose to or** be forced to abandon our **discovery or** development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations **. Preclinical and clinical drug development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies and early clinical trials are not necessarily predictive of future results. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval, and we may choose to terminate development for strategic reasons** . Preclinical and clinical drug development is expensive and can take many years to complete, and its outcome is inherently uncertain. **The historical** ~~Failure~~ **failure rate for product candidates in our industry is high, and failure** can occur at any time during the preclinical study or clinical trial process. Despite promising preclinical or clinical results, any product candidate can unexpectedly fail at any stage of preclinical or clinical development ~~. The historical failure rate~~ **, including termination or abandonment of development** for **strategic reasons** ~~product candidates in our industry is high~~ . The results from preclinical studies or early clinical trials of a product candidate may not predict the results of later clinical trials of the product candidate, and interim, topline or preliminary results of a clinical trial are not necessarily indicative of final results. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy characteristics despite having progressed through preclinical studies and initial clinical trials **or achieving promising early results in earlier studies** . In particular, while we have conducted preclinical studies and have obtained **certain** Phase ~~2~~ **3 topline** results for paltusotine in acromegaly subjects, we do not know how paltusotine will perform in future clinical trials, including **in patients who are not currently receiving medical therapy for acromegaly** ~~as a result of any differences resulting from the use of our new tablet formulation~~ that is in our ongoing Phase 3 clinical trials of paltusotine. It is not uncommon to observe results in clinical trials that are unexpected based on preclinical studies and early clinical trials ~~, and~~ **. Open- label clinical trials are also susceptible to bias that** ~~many~~ **may exaggerate any therapeutic effect or overestimate the risk associated with the product candidate. Furthermore, any safety or efficacy concerns observed in any one of our clinical or non- clinical trials in our targeted indications could limit the prospects for regulatory approval of our** product candidates ~~fail~~ in ~~clinical trials despite very promising early results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses. A number of companies in the~~ **those** ~~pharmaceutical~~ and **other indications** ~~biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies. Furthermore, although our product candidates all target endocrine diseases and / or endocrine- related tumors, we cannot assure you that our preclinical programs will be able to progress from candidate identification to Phase 1 clinical proof- of- concept in healthy volunteers~~ . For the foregoing reasons, we cannot be certain that our ongoing and planned clinical trials and preclinical studies will be successful **, and the failure of** ~~. Any safety concerns observed in~~ any ~~one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of~~ our product candidates ~~in those and other indications, which~~ could have a material adverse effect on our business, financial condition and results of operations **. Any delays in the commencement or completion or any termination or suspension of our clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects** . Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time consuming and uncertain as to outcome. **We may experience delays in clinical trials at any stage of development and testing of our product candidates and any delay could result in increased costs to us. Any clinical trials we undertake may not begin on time, have an effective design, enroll a sufficient number of subjects or be completed on schedule, if at all.** In addition, we may rely in part on preclinical, clinical and quality data generated by clinical research organizations, or CROs, and other third parties for regulatory submissions for our product candidates ~~. While we have~~ **, which carry additional risks as discussed below under the section " Risks related to** ~~or~~ **our reliance on** ~~will have agreements governing these~~ third parties ~~' services, we have limited influence over their actual performance~~ . ~~If~~ **" For example, if** these third parties do not make data available to us, or, if applicable, **do not** make regulatory submissions in a timely manner, in each case pursuant to our agreements with them, our development programs may be significantly delayed, and we may need to conduct additional studies or collect additional data independently. In either case, our development costs would increase. The FDA or comparable foreign regulatory authorities may require us to conduct additional preclinical studies for any product candidate before they allow us to initiate clinical trials under any IND or similar regulatory filing, which may lead to additional delays and increase the costs of our preclinical development programs. ~~For example, in November 2022, the FDA informed us that our IND for CRN04777 was placed on clinical hold and the proposed Phase 2 clinical study may not yet be initiated. Although we believe we will be able to successfully resolve the issues identified by the FDA and initiate our Phase 2 clinical trial, there is no guarantee that the FDA will allow such trial to proceed in a timely manner, or at all. This or any other such delays in the commencement or completion of our ongoing and planned clinical trials for our product candidates could significantly affect our product development costs, which could have a material adverse effect on our business, financial condition and results of operations.~~ We do not know whether our planned trials will begin on time or be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including **the factors discussed elsewhere in this " Risk Factors " section and any** delays **, suspensions, or terminations** related to: • the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical

studies , or declining ~~; • obtaining regulatory authorizations~~ to authorize ~~commence~~ commencing a trial ~~or reaching a consensus with regulatory authorities on trial design~~ ; • any failure or delay in reaching an agreement with CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites; • ~~obtaining approval from one or more~~ institutional review boards, or IRBs ~~; • IRBs~~ , data safety monitoring boards, investigators, or regulators refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing their approval of the trial; • any changes to clinical trial protocol , product candidate formulation, or our manufacturing process that may be necessary or desired, requiring additional preclinical studies or regulatory approval ; • clinical sites deviating from trial protocol or dropping out of a trial; • manufacturing sufficient quantities of product candidate or obtaining sufficient quantities of combination therapies for use in clinical trials; • subjects failing to enroll or remain in our trial at the rate we expect, or failing to return for post- treatment follow- up; • subjects choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials; • lack of adequate funding to continue the clinical trial; • subjects experiencing severe or unexpected drug- related adverse effects; • occurrence of serious adverse events in trials of the same class of agents conducted by other companies; • selection of clinical end points that require prolonged periods of clinical observation or analysis of the resulting data; • negative or inconclusive results from preclinical testing or clinical trials leading to a decision or requirement to conduct additional preclinical testing or clinical trials or abandon a program; • a facility manufacturing our product candidates or any of their components being ordered by the FDA or comparable foreign regulatory authorities to temporarily or permanently shut down due to violations of current good manufacturing practice, or cGMP, regulations or other applicable requirements, or infections or cross- contaminations of product candidates in the manufacturing process ~~; • any changes to our manufacturing process that may be necessary or desired~~ ; • third- party clinical investigators losing the licenses or permits necessary to perform our clinical trials, and not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, good clinical practices, or GCP, or other regulatory requirements; • third- party contractors not performing data collection or analysis in a timely or accurate manner; ~~or~~ • third- party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications ; ~~. In addition, disruptions caused by the COVID- 19 pandemic have and may continue to increase the likelihood that we encounter such difficulties~~ or • delays in ~~initiating, enrolling, conducting, or~~ our ~~completing our planned and ongoing~~ clinical trials resulting from external factors including global conflicts and health epidemics . We could also encounter delays if a clinical trial is suspended or terminated by us or oversight authorities , ~~by~~ including the IRBs of the institutions in which such trials are being conducted, the ~~by a~~ Data Safety Monitoring Board for such trial , or by the FDA or comparable foreign regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. **For example, in November 2022, the FDA informed us that our IND for CRN04777 was placed on clinical hold and the proposed Phase 2 clinical study was not initiated. Although we subsequently discontinued clinical development for CRN04777 in August 2023 for unrelated reasons, any other such delays in the completion of our ongoing and planned clinical trials for our product candidates could significantly affect our product development costs, which could have a material adverse effect on our business, financial condition and results of operations.** In addition, changes in regulatory requirements and policies may occur , including the imposition of additional regulatory oversight around clinical testing generally or with respect to our product candidates in particular , and we may need to amend clinical trial protocols to comply with these changes. Amendments may require us to resubmit our clinical trial protocols to ~~IRBs~~ certain authorities for reexamination, which may impact the costs, timing or successful completion of a clinical trial , and could lead us to delay, reduce, abandon, or terminate development of our product candidates . Further, conducting clinical trials in foreign countries, as we currently are and may continue to do, for our product candidates ~~,~~ presents additional risks that may delay completion of or result in suspension, abandonment or termination of our clinical trials. We must comply with numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials. ~~These~~ -- The foreign regulatory approval process varies among countries, and the time required to obtain approval may differ from that required to obtain FDA approval. Additional risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks, including war, relevant to such foreign countries. ~~For example, we had planned to conduct clinical trials at sites in Russia but paused activities at these sites prior to randomizing patients due to the conflict in Ukraine and the imposition of sanctions against Russia.~~ Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive cash or equity compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates . In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in

the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate . If we experience delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. **Any** ~~Moreover, any~~ delays **to** ~~in completing~~ our clinical trials ~~will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate. We may make formulation or manufacturing changes to our product candidates, in which case we may need to conduct additional preclinical studies to bridge our modified product candidates to earlier versions. Any delays to our clinical trials that occur as a result~~ could shorten any period during which we may have the exclusive right to commercialize our product candidates and our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced. **Moreover, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. We may delay, suspend, abandon or terminate development of our product candidates, or one or more product candidate indications or territories for various strategic reasons.** Any of these occurrences may ~~harm~~ **have a material adverse effect on** our business, financial condition and prospects ~~significantly. The COVID-19 pandemic, related variants and other epidemic diseases has and could continue to adversely impact our business, including our drug manufacturing, nonclinical activities and clinical trials. The COVID-19 pandemic and government measures taken in response have had a significant impact, both direct and indirect, on businesses and commerce. The extent to which the COVID-19 pandemic may impact our business, including our preclinical studies, planned clinical trials, and financial condition will depend on future developments, which are highly uncertain and cannot be predicted with confidence. For example, the recent lifting of COVID-19 restrictions and subsequent COVID-19 outbreaks in China have resulted in delays to our planned recruitment of patients in our PATHFNDR-2 study. Previously, we have experienced certain delays in our clinical trials which resulted in a several month delay in the release of preliminary data from our Phase 1 study of CRN04894 due to the fact that some of the healthy volunteers contracted COVID-19 during a cohort of the multiple ascending dose portion of the study. We continue to actively monitor COVID-19 and may take further actions that alter our operations, including those that may be required by federal, state or local authorities, or that we determine are in the best interests of its employees and other third parties with whom the Company does business. In connection with the COVID-19 pandemic or an outbreak of another highly infectious or contagious disease or other health concern, we may continue to experience disruptions that could severely impact our business, drug manufacturing, nonclinical activities, and clinical trials, including: • delays or difficulties in enrolling volunteers and patients in our clinical trials; • delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and staff; • diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials; • interruption of key clinical trial activities, such as clinical trial site monitoring and source data verification, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures, which may impact the integrity of subject data and clinical study endpoints; • interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines; • interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems; • delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials and interruption in global shipping that may affect the transport of clinical trial materials; • interruptions in nonclinical studies due to restricted or limited operations at our laboratory facility or those of our outsourced service providers; • limitations on employee resources that would otherwise be focused on the conduct of our nonclinical studies or clinical trials due to sickness of employees or their families or the desire of employees to avoid contact with large groups of people, or other staffing shortages as a result of remote working requirements or otherwise; • delays in receiving authorization from local regulatory authorities to initiate our planned clinical trials; • changes in local regulations as part of a response to COVID-19 or other epidemic diseases which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue such clinical trials altogether; • delays in necessary interactions with local regulators, ethics committees, and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees; • refusal of the FDA to accept data from clinical trials in affected geographies outside the United States; • interruption or delays to our discovery and development pipeline; and • patent office interruption or delays in our ability to timely secure patent coverage for our product candidates. In addition, the spread of COVID-19 has impacted and may continue to impact the trading price of shares of our common stock and could further impact our ability to raise additional capital on a timely basis or at all. The extent to which the COVID-19 may impact our business, including our drug manufacturing, nonclinical activities, clinical trials, and financial condition will depend on future developments, which are highly uncertain and cannot be predicted with confidence. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also have the effect of heightening many of the other risks described in this section. In addition, if in the future there is a further outbreak of COVID-19 or a variation thereof, an outbreak of another highly infectious or contagious disease or other health concern, we may be subject to similar risks as posed by COVID-19** . We may find it difficult to enroll **and retain** patients in our clinical trials given the limited number of patients who have the diseases for which our product candidates are being developed. If we encounter difficulties enrolling subjects in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected. **We may not be able to initiate or continue clinical trials if we are unable to identify and enroll a sufficient number of eligible** ~~Subject~~ **subjects to participate in the clinical trials required by the FDA or comparable foreign regulatory authorities. Even once** ~~enrollment~~ **enrolled** , **we**

may be unable to retain a sufficient number of patients to complete any of our trials. This process of finding and enrolling subjects may prove costly and is a significant factor in the timing of clinical trials ~~,~~**. Patient enrollment and retention** is affected by many factors **,** including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility and exclusion criteria for the trial, the design of the clinical trial, the risk that enrolled patients will not complete a clinical trial **, our ability to obtain and maintain patient consents, including any additional consents necessary for enrollment of adolescent patients** , our ability to recruit clinical trial investigators with the appropriate competencies and experience, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating as well as any drugs under development. ~~We will be required to identify and enroll a sufficient number of subjects for each of our clinical trials.~~ Potential subjects for any planned or ongoing clinical trials may not be adequately diagnosed or identified with the diseases which we are targeting ~~or may not meet the entry criteria for such trials. For example~~ , ~~each of our target indications is an~~ **and we** ~~orphan indication and, in particular, our lead product candidate, paltusotine, targets acromegaly, a condition which currently affects approximately 27, 000 people in the United States. We also~~ may encounter difficulties in identifying and enrolling subjects with a stage of disease appropriate for our planned or ongoing clinical trials ~~and monitoring such subjects adequately during and after treatment~~ . **Furthermore, any negative results** ~~We may not be able to initiate~~ or ~~continue~~ **new safety signals we may report in** clinical trials ~~if~~ **of our product candidates may make it difficult or impossible to recruit and retain patients in other clinical trials** we are **conducting. Similarly, results reported by our competitors about** ~~unable to locate a sufficient number of eligible subjects to participate in the~~ **their product candidates may negatively affect patient recruitment in our** clinical trials ~~required by the FDA or comparable foreign regulatory authorities~~ . **We** ~~In addition, the process of finding and diagnosing subjects~~ may ~~prove costly. The timing of~~ **find it difficult to enroll patients in** our clinical trials **because some** ~~depends, in part, on the speed at which we can recruit patients to participate in our trials, as well as completion~~ of **the** ~~required follow- up periods. The~~ conditions for which we currently plan to evaluate our product candidates are orphan or rare diseases with limited patient pools from which to draw for clinical trials. **For example, some of our target indications are orphan indications, and in particular, our product candidate, CRN04894, targets CAH, a condition which currently affects approximately 27, 000 people in the United States.** The eligibility criteria of our clinical trials ~~, once established,~~ will further limit the pool of available trial participants. If **eligible** patients are unwilling to participate in our trials for any reason, including the existence of concurrent clinical trials for similar patient populations, if they are unwilling to enroll in a clinical trial with a placebo- controlled design or the availability of approved therapies, or we otherwise have difficulty enrolling a sufficient number of patients, the timeline for recruiting subjects, conducting studies and obtaining regulatory approval of our product candidates may be delayed. Our inability to enroll a sufficient number of subjects for any of our **current or** future clinical trials would result in significant delays **beyond** ~~or~~ **our expected timelines,** may require us to abandon one or more clinical trials altogether ~~. In~~ **, may result in increased development costs for our product candidates, which could cause the value of our common stock to decline and limit our ability to obtain** ~~addition~~ **additional financing. Additionally** , ~~we expect to rely~~ **the FDA or comparable foreign regulatory authorities may modify or enhance trial requirements, which may affect enrollment. For example, in August 2023, the FDA published a guidance document, " Informed Consent, Guidance for IRBs, Clinical Investigators, and Sponsors, " which supersedes past guidance and finalizes draft guidance** on ~~CROs~~ **informed consent. The FDA' s new guidance presents evolving requirements for informed consent which may affect recruitment** and **retention of patients in clinical trials. Effects on recruitment and retention of patients may hinder or delay a** clinical trial ~~sites~~ **and could cause a significant setback** to ~~ensure proper and~~ - **an applicable program** ~~timely conduct of our future clinical trials and, while we intend to enter into agreements governing their services, we will have limited influence over their actual performance~~ . We cannot assure you that our assumptions used in determining expected clinical trial timelines are correct or that we will not experience delays in enrollment, which would result in the delay of completion of such trials beyond our expected timelines **, and result in a material adverse effect on our business, prospects, financial condition and results of operations** . Use of our product candidates could be associated with side effects or adverse events, which could severely harm our business, prospects, operating results and financial condition. As is the case with pharmaceuticals generally, it is likely that there may be side effects and adverse events associated with our product candidates' use. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates **, or even by other companies' similar approved drugs or product candidates,** could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. The drug- related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. **Additionally, the inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or due to the gravity of such patients' illnesses.** Any of these occurrences may harm our business, financial condition and prospects significantly. Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective, which may limit the commercial expectations for the product candidate if approved. We may also be required to modify our study plans based on findings in our clinical trials. Many compounds that initially showed promise in early **-** stage testing have later been found to cause side effects that prevented further development of the compound. In addition, regulatory authorities may draw different conclusions or require additional testing to confirm these determinations **. Further, we have no control over the clinical trials or development program of third parties developing investigational products directed to the same target as one of our**

programs. Adverse findings or results from any of their clinical trials could adversely affect the commercial prospects of our investigational products and cause our stock price to fluctuate or decline . It is possible that as we test our product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens and formulations, or as the use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition and prospects significantly. In addition, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including: • regulatory authorities may withdraw approvals of such product **or require additional warnings on the label, such as a " black box " warning or a contraindication** ; • we may be required to recall a product or change the way such product is administered to patients ~~; • regulatory authorities may require additional warnings on the label, such as a " black box " warning or a contraindication~~ ; • we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients; • we could be sued and held liable for harm caused to patients; • the product could become less competitive; and • our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could ~~significantly harm~~ **have a material adverse effect on** our business, results of operations and prospects. The **research,** clinical development, **testing, quality control, safety, effectiveness,** manufacturing, labeling **, packaging** , storage, record- keeping, advertising, promotion, **marketing,** import, export, ~~marketing and~~ distribution **, post- approval monitoring, and post- approval reporting** of our product candidates are subject to extensive regulation by the FDA in the United States and by comparable foreign regulatory authorities in foreign markets. In the United States, **neither** we **nor any future collaborators** are ~~not~~ permitted to market our product candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years following the commencement of clinical trials and can vary substantially based upon the type, complexity and novelty of the product candidates involved, as well as the target indications and patient population. Approval policies or regulations may change, **new relevant statutes or regulations may be enacted,** and the FDA ~~has~~ **and comparable foreign regulatory authorities have** substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed ~~. Neither we nor any future collaborator is permitted to market any of our product candidates in the United States until we receive approval of an NDA from the FDA~~ . Prior to obtaining approval to commercialize a product candidate in the United States or abroad, we or our potential future collaborators must demonstrate with substantial evidence from adequate and well- controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such product candidates are safe and effective for their intended uses. Results from nonclinical studies and clinical trials can be interpreted in different ways. Even if we believe the nonclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and comparable foreign regulatory authorities **, which could require us to delay or abandon clinical development plans** . For example, while we **have completed one and** are **currently** conducting ~~two~~ **a second** Phase 3 clinical ~~trials~~ **trial** of paltusotine in distinct patient populations (patients who are on stable doses of ~~SRL~~ **SRLs** monotherapy and patients who are not being treated with pharmacotherapy), the FDA or comparable foreign regulatory authorities may require additional clinical trials or suggest changes to our planned clinical trials, prior to and in support of the approval of an NDA or equivalent foreign marketing application. ~~The~~ **Further, requirements regarding clinical trial data may evolve. For example, in June 2023, the FDA published a draft guidance, E6 (R3) Good Clinical Practice, which seeks to unify standards for clinical trial data for ICH member countries and regions. Changes to data requirements by the** FDA or comparable foreign regulatory authorities, as the case may be, may ~~also~~ **cause the applicable regulatory authorities to** require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post- approval, or may object to elements of our clinical development program. The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including: • such authorities may disagree with the design or implementation of our clinical trials; • negative or ambiguous results from our clinical trials or results may not meet the level of statistical significance required by the FDA or comparable foreign regulatory agencies for approval; • serious and unexpected drug- related side effects may be experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates; • the population studied in the clinical trial may not be sufficiently broad or representative to assure safety in the full population for which we seek approval; • such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States; • we may be unable to demonstrate that a product candidate' s clinical and other benefits outweigh its safety risks; • such authorities may disagree with our interpretation of data from preclinical studies or clinical trials; ~~•~~ such authorities may not agree that the data collected from clinical trials of our product candidates are acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere, and such authorities may impose requirements for additional preclinical studies or clinical trials; • such authorities may disagree regarding the formulation, labeling and / or the specifications of our product candidates; • approval may be granted only for indications that are significantly more limited than what we apply for and / or with other significant restrictions on distribution and use; • such authorities may find deficiencies in the manufacturing processes or facilities of our third- party manufacturers with which we or any of our potential future collaborators contract for clinical and commercial supplies; or • the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our potential future collaborators' clinical data insufficient for approval. With respect to foreign markets, approval procedures vary among countries and, in addition to the foregoing risks, may involve additional product testing, administrative

review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed pharmaceuticals may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Any delay in obtaining, or inability to obtain, applicable regulatory approvals would prevent us or any of our potential future collaborators from commercializing our product candidates. Of the large number of drugs in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our product candidates, which would significantly harm our business, financial condition, results of operations and prospects. Even if we eventually complete clinical trials and receive approval of an NDA or foreign marketing application for our product candidates, the FDA or comparable foreign regulatory authority may grant approval contingent on the performance of costly additional clinical trials, including Phase 4 clinical trials ~~, and /~~ or the implementation of a REMS, which may be required to ensure safe use of the drug after approval. The FDA or the comparable foreign regulatory authority also may approve a product candidate for a more limited indication or patient population than we originally requested, and the FDA or comparable foreign regulatory authority may not approve the labeling that we believe is necessary or desirable for the successful commercialization of a product. ~~Any delay in obtaining,~~ **These additional limitations could adversely affect** ~~or~~ **our** ~~inability --~~ **ability** to **generate revenue from sales** ~~obtain, applicable regulatory approval would delay or prevent commercialization~~ of ~~that~~ **those** ~~product~~ **products** ~~candidate~~ and ~~would~~ **could** materially adversely impact our business and prospects ~~. We may expend our limited resources to pursue a particular product candidate and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success~~ . Because we have limited financial and managerial resources, we focus on specific product candidates, indications and discovery programs. ~~As~~ **We may expend our limited resources to pursue a particular product candidate, and as** a result, we may **abandon, terminate,** forgo or delay pursuit of opportunities with other product candidates **or in other indications and territories** that could have had greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through future collaborations, licenses and other similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. We have obtained orphan drug designation from the FDA for paltusotine for the treatment of acromegaly ~~and have received orphan drug designation from the EMA for CRN04777 for the treatment of congenital HI~~ . We also plan to seek orphan drug designations for certain of our other product candidates. However, we may not be able to obtain or maintain orphan drug designations for any of our product candidates, and we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product as an orphan product if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200, 000 individuals in the United States, or a patient population of greater than 200, 000 individuals in the United States, but for which there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA ~~' ~~**'** s Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life- threatening or chronically debilitating condition affecting not more than five in 10, 000 persons in the European Union. We have obtained orphan drug designation for paltusotine in the United States for the treatment of acromegaly, and we ~~intend to seek~~ **are considering seeking** a similar orphan drug designation in the European Union **and other territories** . We ~~have~~ **may** also ~~obtained orphan drug designation for CRN04777 in Europe for the treatment of congenital HI. We also plan to~~ seek orphan drug designations for certain of our other product candidates. There can be no assurance, however, that the FDA or the EMA' s Committee for Orphan Medicinal Products will grant orphan designation for any indication for which we apply. **Even if we do receive such designations, we do not know if, when, or how the FDA or the EMA may change the orphan drug regulations and policies in the future. The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term " same disease or condition " means the designated " rare disease or condition " and could not be interpreted by the FDA to mean the " indication or use. " Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan- drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA or Congress may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted. Additionally, on April 26, 2023, the European Commission adopted a proposal for a new Directive and a new Regulation, and in October 2023, the European Parliament proposed further revisions. If made into law, this proposal will revise and replace the existing general pharmaceutical legislation and may make it more difficult to obtain orphan designation in from the EMA and reduce baseline exclusivity periods.** In the United States, orphan designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user- fee waivers. **Despite this designation, we may be unable to maintain the benefits associated with orphan drug status, including market exclusivity.** In addition, if a product candidate that has orphan designation subsequently receives the first

FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. The applicable exclusivity period is ten years in Europe, but such exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA or comparable foreign regulatory authority can subsequently approve the same drug for the same condition if such regulatory authority concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process ~~. The FDA has granted rare pediatric disease designation for CRN04777 for the treatment of congenital HI, however, there is no guarantee that FDA approval of CRN04777 will result in a priority review voucher. In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a " rare pediatric disease " that meets certain criteria may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U. S. within one year following the date of approval. The FDA has granted rare pediatric disease designation for CRN04777 for the treatment of congenital HI, however, there is no guarantee that we will be able to obtain a priority review voucher, even if CRN04777 is approved by the FDA. Moreover, Congress included a sunset provision in the statute authorizing the rare pediatric disease priority review voucher program. Specifically, FDA may not award the voucher to sponsors of marketing applications unless either (i) the drug has received rare pediatric disease designation as of September 30, 2024 and is then approved by the FDA no later than September 30, 2026; or (ii) Congress reauthorizes the program. Even though we received rare pediatric disease designation for CRN04777 by the current statutory deadline of September 30, 2024 we may not receive the voucher if we do not obtain approval by September 2026. Even if legislation is enacted that extends the date by which approval of the rare pediatric disease- designated drug must obtain approval to receive a priority review voucher, we may not obtain approval by that date, and even if we do, we may not obtain a priority review voucher. We have conducted, and continue to conduct, clinical trials for our product candidates outside of the United States and we may do so for our other product candidates. However, the FDA and other foreign equivalents may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business~~ . We are conducting, and may in the future conduct, certain of our clinical trials at centers outside of the United States. The acceptance of study data from clinical trials conducted outside the U. S. or another jurisdiction by the FDA or a comparable foreign regulatory authority may be subject to certain conditions or may not be accepted at all. For example, in cases where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the U. S., the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U. S. population and U. S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and (iii) the data may be considered valid without the need for an on- site inspection by the FDA, or if the FDA considers such inspection to be necessary, the FDA is able to validate the data through an on- site inspection or other appropriate means. In addition, even where the foreign study data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the study is well- designed and well- conducted in accordance with GCP requirements and the FDA is able to validate the data from the study through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. If the FDA, U. K. Medicines and Healthcare products Regulatory Agency, or MHRA, or other foreign equivalents do not accept any data generated from other jurisdictions, we would likely be required to conduct additional clinical trials, which would be costly and time consuming, and delay aspects of our development plan, which could harm our business. Conducting trials outside the United States also exposes us to additional risks, including risks associated with: • additional foreign regulatory requirements; • foreign exchange fluctuations; • compliance with foreign manufacturing, customs, shipment and storage requirements; • cultural differences in medical practice and clinical research; • diminished protection of intellectual property in some countries; and • interruptions or delays in our trials resulting from geopolitical events, such as war or terrorism. In ~~particular, we had planned to conduct our PATHFNDR- 1 and PATHFNDR- 2 trials of paltusotine in acromegaly patients at sites in Russia, but suspended our enrollment efforts for the foreseeable future at such sites. As a result of Russia' s invasion of Ukraine in February 2022, the United States and its European allies have imposed significant sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. Our ability to conduct clinical trials in Russia and elsewhere in the region may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, which may increase our development costs and delay the clinical development of our product candidates. All of the foregoing could impede the execution of our clinical development plans, which could materially harm our business. In~~ addition, effective January 31, 2020, the United Kingdom commenced an exit from the European Union, commonly referred to as " Brexit " and, following the expiration of the Brexit transitional period on December 31, 2020, operates under a distinct regulatory regime.

European legislation ~~, including on clinical trials (including the impending EU Clinical Trials Regulation, or EU CTR),~~ is no longer directly applicable in the United Kingdom. Current United Kingdom rules on clinical trials are derived from ~~existing~~ **prior** European Union legislation (as implemented into United Kingdom law), ~~however~~ **and** going forward there is a risk that United Kingdom rules will **continue to** diverge from European Union laws. **For example,** ~~Although regulatory authorities in~~ the **EU Clinical Trials Regulation, or EU CTR, effective on January 31, 2022 provides for a streamlined clinical trial application and assessment procedure covering multiple EU Member States. However, this has not been implemented into** United Kingdom **law** ~~have indicated in the Medicines and Medical Devices Bill that new United Kingdom rules will closely align with the European Union legislation~~ , ~~detailed proposals are yet to~~ **and a separate application must** be **submitted** ~~published. In addition, already as a result of the United Kingdom ceasing to be part of the European Union, various benefits of membership no longer apply to the United Kingdom, such that, for example, United Kingdom sponsored trials that span several European countries now need to have an individual or organization in the European Union to act as a legal representative, or sponsor; it is unclear whether the United Kingdom will have access to European Union clinical trial databases such as the Clinical Trial Information System (the centralized EU Portal~~ for clinical trial ~~information storage~~ **authorization in the United Kingdom. In addition, Great Britain is no longer covered by the centralized procedure for obtaining EEA- wide marketing authorizations from the EMA for medicinal products and a separate process for authorization of drug products is required in Great Britain. Until December 31, 2023, the U. K.' s MHRA could rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization, however a separate application was still required. From January 1, 2024, a new international recognition framework will be put in place in the U. K. (which will be known as the International Recognition Procedure, or IRP**) ~~;~~ **, whereby the MHRA will have regard to decisions made by certain foreign regulators, including the EMA** and **the competent authorities of the EU Member States. Under this procedure, the MHRA will take into account the decision- making of such foreign regulators and will conduct a targeted assessment of the applications submitted through the IRP, but will retain the authority to reject applications if the evidence provided is considered insufficiently robust.** ~~additionally~~ **Additionally** , new rules apply to the import of investigational medicinal products from the European Union and European Economic Area to the United Kingdom. As a result, Brexit may create additional administrative burdens including disruptions to and uncertainty surrounding our planned clinical trials and activities in the United Kingdom and the European Union, impacting relationships with our existing and prospective customers, partners, vendors and employees. Although the United Kingdom and European Union have now reached an agreement on their future trading relationship to be implemented in the EU- UK Trade and Cooperation Agreement from January 1, 2021, which includes zero tariffs on goods and provides for regulatory cooperation, the agreement does not cover all regulatory areas regarding supply of medicinal products, which will likely be subject to bilateral discussions going forward which could further change the relationship between the United Kingdom and the European Union in this regard. **Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would delay or prevent us from commercializing our current or future product candidates in the U. K. and could restrict our ability to generate revenue from that market.** Changes impacting our ability to conduct business in the United Kingdom or other European Union countries, or changes to the regulatory regime applicable to our operations in those countries (such as with respect to the approval of our product candidates), may have a material adverse impact on our business, financial condition and prospects. **One of** ~~Interim, topline and preliminary data from~~ our **sites in our PATHFNDR- 2** clinical ~~trials~~ **trial** ~~that we announce or~~ **for** ~~publish from~~ **paltusotine is located in Israel, and the Israel- Hamas war may cause interruption or suspension of this site without warning, or otherwise negatively impact the global economy or our business. One of our sites in our PATHFNDR- 2 clinical trial for paltusotine is located in Israel and has one currently enrolled patient. As of December 31, 2023, the Israel- Hamas war has not impacted the execution of the study or care of the enrolled patient however, the intensity, duration and short and long- term implications of the Israel- Hamas war are difficult to predict at this** time ~~to time~~ **. Additionally, a prolonged conflict** may **impact the global economy and result in, among other things, increased inflation, supply chain shortages and declines in economic growth. The war may also have the effect of heightening other risks to our business including, but not limited to, adverse effects on macroeconomic conditions, including inflation ; disruptions to our global technology infrastructure, including through cyberattack, ransom attack, or cyber- intrusion ; adverse** ~~change~~ **changes in international trade policies** ~~as more patient data become available~~ and ~~are subject to audit~~ **relations ; disruptions in global supply chains ;** and ~~verification procedures that~~ **constraints, volatility, or disruption in the capital markets, any of which** could ~~result in~~ **have a** material ~~changes in the final data~~ **adverse effect on our business and financial condition** . From time to time, we may publicly disclose **initial, interim,** preliminary or topline or data from our clinical studies, which is based on a preliminary analysis of then- available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the **initial, topline or other** preliminary ~~or topline~~ results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Preliminary and topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, **interim, topline or other** preliminary ~~and topline~~ data should be viewed with caution until the final data are available. From time to time, we may also disclose **initial or** interim data from our clinical studies. **Initial and** ~~Interim~~ **interim** data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between **initial,** preliminary, topline or interim data and final data could significantly harm our business prospects. ~~Further~~ **Moreover** ,

preclinical and clinical data are often susceptible to varying interpretations and analyses. ~~others~~ **Others**, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular drug, drug candidate or our business. If the interim, preliminary, or topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition. ~~Risks related to our reliance on third parties~~ We rely on third parties to conduct many of our preclinical studies and clinical trials. Any failure by a third party to conduct the clinical trials according to GCPs and in a timely manner may delay or prevent our ability to seek or obtain regulatory approval for or commercialize our product candidates. We are dependent on third parties to conduct our preclinical studies and clinical trials, including our clinical trials for paltusotine, ~~CRN04777,~~ CRN04894, and any future clinical trials and preclinical studies for our product candidates. ~~Specifically~~ **For example**, we have used and relied on, and intend to continue to use and rely on, medical institutions, clinical investigators, **partners, licensees, clinical data management organizations,** CROs **, trial sites,** and consultants **, among others,** to conduct our clinical trials in accordance with our **trial design,** clinical protocols and regulatory requirements. These CROs, investigators and other third parties play a significant role in the conduct and timing of these trials and subsequent collection and analysis of data. While we have agreements governing the activities of our third- party contractors, we have limited influence over their actual performance. Nevertheless, we are responsible for ensuring that each of our **pre- clinical and** clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our product candidates in clinical development. **We must also ensure that our preclinical trials are conducted in accordance with the FDA' s Good Laboratory Practice regulations, as appropriate.** Regulatory authorities enforce these ~~GCPs~~ **requirements** through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs or trial sites fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. There is no guarantee that any such CROs, investigators or other third parties will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. In addition, many of the third parties with whom we contract may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. ~~In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA concludes that the financial relationship may have affected the interpretation of the study, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of any NDA we submit by the FDA. Any such delay or rejection could prevent us from commercializing our product candidates.~~ If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third parties or do so on commercially reasonable terms **or in a time frame acceptable to us**. **Even if we are able to enter into alternative arrangements,** ~~Switching~~ **switching** or adding additional CROs, investigators and other third parties involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, investigators and other third parties, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects. We do not own or operate manufacturing facilities and have no plans to build our own clinical or commercial scale manufacturing capabilities. We rely, and expect to continue to rely, on third parties for the manufacture **and supply** of our product candidates and related raw materials for preclinical and clinical development, as well as for commercial manufacture if any of our product candidates receive marketing approval. Furthermore, the raw materials for our product candidates are sourced, in some cases, from a single- source supplier. If we were to experience an unexpected loss of **or interruption to** supply of any of our product candidates or any of our future product candidates for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing clinical trials. **We** ~~For example, the extent to which the COVID- 19 pandemic impacts our ability to procure sufficient supplies for the development of our products and product candidates~~ will depend on ~~future developments, which are highly uncertain and cannot be predicted~~ **these third parties to perform their obligations in a timely manner consistent** with ~~confidence~~ **contractual and regulatory requirements, including those related to quality control and assurance**. ~~The~~ **For example, the** facilities used by third- party manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we

submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, third- party manufacturers for compliance with cGMP requirements for manufacture of drug products. If these third- party manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, including requirements related to the manufacturing of high potency compounds, they will not be able to secure and / or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of third- party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates ~~,~~ if approved. Our failure, or the failure of our third- party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products **. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval, and any related remedial measures may be costly or time- consuming to implement. We do not currently have arrangements in place for redundant supply or a second source for all required raw materials, API, and intermediaries used in the manufacture of our product candidates. If our current third- party suppliers and manufacturers cannot perform as agreed, we may be required to replace such third parties, and we may be unable to replace them on a timely basis or at all. If we are required to change suppliers or manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines** . In addition, we may be unable to establish any agreements with third- party **suppliers or** manufacturers or to do so on acceptable terms **. The delays associated with the onboarding of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget** . Even if we are able to establish agreements with third- party manufacturers, reliance on third- party **suppliers and** manufacturers entails additional risks, including: • failure of third- party **suppliers and** manufacturers to comply with regulatory requirements and maintain quality assurance; • breach of the **supply or** manufacturing agreement by the third party; • failure to **supply or** manufacture our product according to our specifications; • failure to **supply or** manufacture our product according to our schedule or at all; • **failure of third- party suppliers and manufacturers to maintain a sufficient supply of materials and ingredients necessary to conduct their operations; • inability of a third- party manufacturer to scale up the process in order to produce commercial quantities of our products if approved; •** misappropriation of our proprietary information, including our trade secrets and know- how; ~~and~~ • termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us **; and • external events that may impact the ability of our third- party supplier and manufacturer located outside of the United States to perform and to manufacture our product** . Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. ~~Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval, and any related remedial measures may be costly or time- consuming to implement. We do not currently have arrangements in place for redundant supply or a second source for all required raw materials used in the manufacture of our product candidates. If our current third- party manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all.~~ Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may **materially and** adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis **, which would have a material adverse effect on our business, reputation and prospects** . We are dependent on an international third- party licensee for the development and commercialization of paltusotine in Japan, and **we** may ~~do so~~ **enter into similar agreements** in other geographic regions. The failure of this and other third parties to meet their contractual, regulatory or other obligations could adversely affect our business. We have entered into an exclusive license agreement with Sanwa that provides Sanwa with exclusive rights to the development and commercialization of paltusotine in Japan. As a result, we are dependent on Sanwa to achieve regulatory approval of paltusotine for marketing in Japan and for the commercialization of paltusotine **in Japan** , if approved. The timing and amount of any milestone and royalty payments we may receive under this agreement ~~, as well as the commercial success of paltusotine in Japan,~~ will depend on, among other things, the efforts ~~,~~ **and** allocation of resources and successful commercialization of paltusotine **in Japan** by Sanwa. We also depend on Sanwa to comply with all applicable laws ~~relative~~ -- **related** to the development and commercialization of our product in Japan. **For example,** ~~They~~ **they** may take actions or fail to take actions that result in safety issues with the licensed product in the licensed territory, and such safety issues could negatively impact the licensed product in countries outside of the licensed territory. We do not control the individual efforts of Sanwa **,** and **we** have limited ability to terminate these agreements or to have assigned assets returned to us if Sanwa does not perform as anticipated. The failure of Sanwa to devote sufficient time and effort to the development and commercialization of paltusotine; to meet its obligations to us, including for future royalty and milestone payments; to adequately deploy business continuity plans in the event of a crisis; ~~and /~~ or to satisfactorily resolve significant disagreements with us or address other factors could have an adverse impact on our financial results and operations. In addition, if Sanwa violates, or is alleged to have violated, any laws or regulations during the performance of its obligations for us, including with respect to safety, patient and data privacy, antitrust, and bribery and corruption, it is possible that we could suffer financial and reputational harm or other negative outcomes, including possible legal consequences and liabilities. We may not be successful in enforcing the terms and conditions of our license agreement in court or via agreed upon dispute resolution mechanisms, and even if we were to prevail in any such dispute, the remedies may not be adequate to compensate us for the

losses. Any termination, breach or expiration of any of this license agreement could have a material adverse effect on our financial position by reducing or eliminating the potential for us to receive license fees, milestones and royalties. In such an event, we may be required to devote additional efforts and to incur additional costs associated with pursuing regulatory approval and commercialization of the applicable products and product candidates **in Japan** . Alternatively, we may attempt to identify and transact with a new assignee or licensee, but there can be no assurance that we would be able to identify a suitable partner or transact on terms that are favorable to us. In addition, we may enter into similar license agreements with additional third parties for paltusotine or our other product candidates in other geographic regions, and similar risks would be associated with any such similar arrangements. Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed. Because we currently rely on other third parties ~~to~~ **in the discovery, development, and** manufacture **of** our product candidates ~~and to perform quality testing~~ , we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into **non- disclosure and** confidentiality agreements, consulting agreements or other similar agreements with our advisors, employees ~~and~~ **,** consultants **, contractors, investigators, advisors, collaborators, manufacturers, suppliers, and other third parties** prior to ~~beginning research or~~ disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information **. For example, these agreements typically restrict the ability of the third parties to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with in the future may be granted rights to publish data arising out of such collaboration, subject to certain notice and publication delay requirements in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication** . Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are intentionally or inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know- how and trade secrets and despite our efforts to protect our ~~trade secrets~~ **proprietary information** , a competitor' s discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, financial condition, results of operations and prospects. Risks related to commercialization of our product candidates Even if we receive regulatory approval for any product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions on marketing or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved. Following potential approval of any our product candidates, the FDA **or comparable foreign regulatory authorities** may impose significant restrictions on a product' s indicated uses or marketing or impose ongoing requirements for potentially costly and time- consuming post- approval studies, post- market surveillance or clinical trials to monitor the safety and efficacy of the product. ~~The~~ **For example, the** FDA may also require **the implementation of** a REMS as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for our products will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post- marketing information and reports, registration, as well as continued compliance with cGMPs and GCP requirements for any clinical trials that we conduct post- approval. Later discovery of previously unknown problems with..... response and could generate negative publicity. In addition, **the** ~~if any of our product candidates is approved, our product labeling, advertising and promotion will be subject to regulatory requirements and continuing regulatory review. The~~ FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product' s approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off label uses, we may become subject to significant liability. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses, and a company that is found to have improperly promoted off- label uses may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off- label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. **Later discovery of** previously unknown problems with our products,including adverse events of unanticipated severity or frequency,or with our third- party manufacturers or manufacturing processes,or failure to comply with regulatory requirements,may result in,among other things:• restrictions on the marketing or manufacturing of our products,withdrawal of the product from the market or voluntary or mandatory product recalls;• restrictions on product distribution or use,or requirements to conduct post- marketing studies or clinical trials;• fines,restitutions,disgorgement of profits or revenues,warning letters,untitled letters or holds on clinical trials;• refusal by the FDA ~~or comparable foreign regulatory authorities~~ to approve pending applications or supplements to approved applications filed by us or suspension or revocation of approvals;• product seizure or detention,or refusal to permit the import or export of our products;and The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue and could require us to expend significant time and resources in response and could generate negative **publicity.** The FDA' s and other regulatory

authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay **commercialization** ~~regulatory approval~~ of our product candidates ~~. We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad~~ . If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action, ~~and~~ **as a result of which** we may not achieve or sustain profitability **, which would have a material adverse effect on our business, reputation, prospectus and financial condition** . Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved, or commercialized in a timely manner or at all, which could negatively impact our business. The ability of the FDA **and other government agencies** to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory and policy changes, the FDA' s ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA' s ability to perform routine functions. Average review times at the FDA 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 and biologics or modifications to approved drugs and biologics to be reviewed and / or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, 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. Separately, in response to the COVID- 19 pandemic, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points. Even though the FDA has since resumed standard inspection operations of domestic facilities where feasible, **any resurgence of** the ~~FDA has continued~~ **virus or emergence of new variants may lead** to **further** ~~monitor and implement changes to its~~ inspectional **delays. Further, regulatory authorities outside** ~~activities to ensure the safety of its employees and those~~ -- **the** ~~of~~ **United States may adopt similar restrictions or** ~~the~~ **other policy measures in response** ~~firms it regulates as it adapts~~ to the ~~evolving~~ COVID- 19 pandemic ~~, and any resurgence of the virus or emergence of new variants may lead to further inspectional delays. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID- 19 pandemic,~~ or any other pandemic or outbreak of a contagious disease. 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. The commercial success of our product candidates will depend upon the degree of market acceptance of such product candidates by physicians, patients, health care payors and others in the medical community. Our product candidates may not be commercially successful. Even if any of our product candidates receive regulatory approval, they may not gain market acceptance among physicians, patients, healthcare payors or the medical community. The commercial success of any of our current or future product candidates will depend significantly on the broad adoption and use of the resulting product by physicians and patients for approved indications. The degree of market acceptance of our products will depend on a number of factors, including: • demonstration of clinical efficacy and safety compared to other more- established products; • **our ability to differentiate our product against other approved products; •** the indications for which our product candidates are approved; • the limitation of our targeted patient population and other limitations or warnings contained in any **labeling approved by the** FDA ~~- approved labeling~~ **or other applicable regulatory authorities** ; • acceptance of a new drug for the relevant indication by healthcare providers and their patients **; • the relative convenience and ease of administration of our products** ; • the pricing and cost- effectiveness of our products, as well as the cost of treatment with our products in relation to alternative treatments and therapies; • our ability to obtain and maintain sufficient third- party coverage and adequate reimbursement from government healthcare programs, including Medicare and Medicaid, private health insurers and other third- party payors; • the willingness of patients to pay all, or a portion of, out- of- pocket costs associated with our products in the absence of sufficient third- party coverage and adequate reimbursement; • the prevalence and severity of any adverse effects; • potential product liability claims; • the timing of **regulatory approvals and** market introduction of our products as well as competitive drugs; • the **terms of any approvals and the countries in which approvals are obtained; • the** effectiveness of our or any of our potential future collaborators' sales and marketing strategies; and • ~~unfavorable~~ **the** ~~publicity~~ --- **public** ~~relating to the~~ **perception regarding any** ~~product~~ **products we may develop** . If any product candidate is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors or patients, we may not generate sufficient revenue from that product and may not become or remain profitable. Our efforts to educate the medical community and third- party payors regarding the benefits of our products may require significant resources and may never be successful **, which could have material adverse effect on our business, prospectus, reputation and financial condition** . The successful commercialization of our product candidates, if approved, will depend in part on the extent to which governmental authorities and health insurers establish coverage, adequate reimbursement levels and favorable pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our products could limit our ability to market those products and decrease our ability to generate revenue. The availability of coverage and the adequacy of reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third- party payors are essential for most patients to be able to afford prescription medications such as our product candidates, if approved. Our ability to achieve coverage and acceptable levels of reimbursement for our products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize those products. Even if we obtain coverage for a given product by a third- party payor, the resulting reimbursement payment rates may not be adequate or may require co- payments that patients find unacceptably high. We cannot

be sure that coverage and reimbursement in the United States, the European Union or elsewhere will be available for any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future. Third- party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third- party payors may refuse to provide coverage and reimbursement for particular drugs when an equivalent generic drug or a less expensive therapy is available. It is possible that a third- party payor may consider our products as substitutable and only offer to reimburse patients for the less expensive product. Even if we are successful in demonstrating improved efficacy or improved convenience of administration with our products, pricing of existing drugs may limit the amount we will be able to charge for our products. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our products and may not be able to obtain a satisfactory financial return on products that we may develop. There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, third- party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs will be covered. Some third- party payors may require pre- approval of coverage for new or innovative devices or drug therapies before they will reimburse health care providers who use such therapies. It is difficult to predict at this time what third- party payors will decide with respect to the coverage and reimbursement for our products. Obtaining and maintaining reimbursement status is time- consuming, costly and uncertain. The Medicare and Medicaid programs increasingly are used as models for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs. However, no uniform policy for coverage and reimbursement for products exists among third- party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time- consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely. Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost- containment initiatives in Europe and other countries has and will continue to put pressure on the pricing and usage of our products. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medical products but monitor and control company profits. ~~Additional foreign price controls or other changes~~ **Changes** in pricing regulation **and exchange rates** could restrict the amount that we are able to charge for our products. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits. Moreover, increasing efforts by governmental and third- party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our products. We expect to experience pricing pressures in connection with the sale of any of our products due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. **In addition** ~~As a result~~ , ~~increasingly high barriers~~ **communications from government officials, media outlets, and others regarding health** ~~are~~ **care** ~~being erected to the entry of new~~ **costs and pharmaceutical pricing could have a negative impact on our stock price, even if such communications do not ultimately impact coverage or reimbursement decisions for our** products. The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates. Our competitors have developed, are developing or may develop products, product candidates and processes competitive with our product candidates. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may attempt to develop product candidates **, and which may lead us to abandon one or more product candidates, indications, or territories** . In particular, there is intense competition in the field of endocrine disorders. Our competitors include larger and better funded pharmaceutical, biopharmaceutical, biotechnological and therapeutics companies. Moreover, we may also compete with universities and other research institutions who may be active in endocrinology research and could be in direct competition with us. We also compete with these organizations to recruit management, scientists and clinical development personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites, enrolling subjects for clinical trials and in identifying and in- licensing new product candidates. Smaller or early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. With respect to paltusotine, injected peptide somatostatin agonists and GH receptor antagonists are the main medical therapies for acromegaly patients where surgery is unsuccessful. There are three ~~branded~~ injected somatostatin analogs approved for the treatment of acromegaly: octreotide (marketed by Novartis AG), lanreotide (marketed by Ipsen Biopharmaceuticals, Inc.) and pasireotide (marketed by Recordati Rare Diseases Inc.). **Oral octreotide (marketed by Chiesi Farmaceutici) is approved in the U. S. for the long- term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide.** Pegvisomant (marketed by Pfizer Inc.) is a daily injectable growth hormone receptor antagonist and is generally used in patients not fully controlled on somatostatin analogs. Orally administered dopamine agonists, such as bromocriptine and cabergoline, are also used. In ~~2020, Chiasma, Inc. (Chiasma~~

~~acquired by Amryt Pharma, Aug 2021) received marketing approval in the United States for an oral octreotide product, MYCAPSSA, for long- term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide. In~~ December 2021, the FDA approved a lanreotide injection biosimilar manufactured by Cipla Ltd. for the treatment of acromegaly and GEP- NETs. Other products in clinical development include new formulations of peptide somatostatin agonists ~~or~~ **(Camurus AB) and** GH receptor antagonists **(** ~~. Other companies developing new pharmaceutical therapies for acromegaly include Camurus AB, Ionis Pharmaceuticals, Inc. / Antisense Therapeutics Ltd., Aquestive Therapeutics, Inc., XERIS Pharmaceuticals,~~ Amolyt Pharma ~~and Rani Therapeutics, Inc. With respect to congenital HI, maintaining glucose levels through feeding or glucose infusions is the first step in managing the disease. Diazoxide (marketed by Teva Pharmaceuticals, Inc.~~) ~~is the only approved therapy indicated for hyperinsulinemia. Octreotide (used off- label) is administered as subcutaneous injections in those who respond poorly to diazoxide. Patients who fail pharmacological therapy often progress to partial or nearly complete pancreatectomy, which can result in type I diabetes that must be managed for the remainder of the patient' s life. Ready- to- use glucagon analog products have also been approved and could be used to treat congenital HI if a patient experiences severe hypoglycemia and includes Zegalogue, which received approval in 2021 and is marketed by Zealand Pharma A / S, and Gvoke HypoPen which received approval in 2019 and is marketed by Xeris Pharmaceuticals, Inc,. Companies developing products for potential use in congenital HI include Rezolute, Inc., Hanmi Pharmaceuticals, Eiger Biopharmaceuticals, Inc., Sosei Heptares and AmideBio. As with acromegaly, first- line therapy for Cushing' s disease is surgery to remove the pituitary tumor if possible. Adrenal enzyme inhibitors (metyrapone, ketoconazole) prevent the synthesis of cortisol and can improve symptoms. Mifepristone (marketed by Corcept Therapeutics, Inc.), a glucocorticoid receptor antagonist, is approved for control of hyperglycemia in Cushing' s syndrome. Osilodrostat (marketed by Recordati), a cortisol synthesis inhibitor, is approved for the treatment of endogenous Cushing' s syndrome. The somatostatin agonist pasireotide is also approved for Cushing' s disease. Strongbridge Biopharma is conducting a Phase 3 clinical trial with levoketoconazole, respectively. Other companies developing products for potential use in Cushing' s disease include Corcept Therapeutics, Inc., and Cyclacel Pharmaceuticals, Inc. Neurocrine Biosciences and Spruce Biosciences are developing CRF receptor antagonists for the treatment of CAH~~ . Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we do. If we successfully obtain approval for any product candidate, we will face competition based on many different factors, including the safety and effectiveness of our products, the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration, the timing and scope of regulatory approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, including by being more effective, safer, more convenient, less expensive or marketed and sold more effectively than any products we may develop. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. For example, a competitor could develop another oral formulation of a somatostatin agonist or other technology that could make administration of peptide therapies more convenient. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our products we may develop, if approved, could be **material and** adversely affected **, which would material adversely affect our results of operations, financial condition and business** . The ~~number~~ **numbers** of patients suffering from the rare endocrine diseases **and endocrine- related tumors** that we target is small ~~,~~ and have not been established with precision. If the market opportunities for our products are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. We focus our research and product development on treatments for orphan and rare diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our products, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including ~~the~~ scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. **If any of our estimates are** ~~The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately~~ -- **inaccurate** ~~predict~~ **,** the **market opportunities** ~~number of patients~~ for ~~whom treatment might~~ **any of our product candidates could** be ~~possible~~ **significantly diminished** . Additionally, the potentially addressable patient population for each of our products may be limited or may not be amenable to treatment with our products, and new patients may become increasingly difficult to identify or gain access to ~~, which would adversely affect our results of operations and our business~~ . Further, even if we obtain significant market share for our products, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share **. Any of the foregoing would materially and adversely affect our results of operations and our business** . We may seek to enter into collaborations, licenses and other similar arrangements of our product and may not be successful in doing so, and even if we are, we may not realize the benefits of such relationships. We may seek to enter into collaborations, licenses and other similar arrangements for the development or commercialization of our product candidates, due to capital costs required to develop or commercialize the product candidate in such markets. We may not be successful in our efforts to establish such collaborations for our product candidates because our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy or significant commercial opportunity. In addition, we face significant competition in seeking appropriate strategic partners, and the negotiation process can be time- consuming and complex. Further, we may have to relinquish valuable rights to our future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us, as part of any such arrangement, and such arrangements may restrict us from entering into additional agreements with potential collaborators. We cannot be certain

that, following a strategic transaction or license, we will achieve an economic benefit that justifies such transaction. Even if we are successful in our efforts to establish such collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such collaborations if, for example, development or approval of a product candidate is delayed, the safety of a product candidate is questioned, or sales of an approved product are unsatisfactory. We also may not be able to realize the benefit of such collaborations if we are unable to successfully integrate them with our existing operations and company culture. In addition, any potential future collaborations may be terminable by our strategic partners, and we may not be able to adequately protect our rights under these agreements. Furthermore, strategic partners may negotiate for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do. Any termination of collaborations we enter into in the future, or any delay in entering into collaborations related to our product candidates, could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market, which could have a material adverse effect on our business, financial condition and results of operations. We currently have no ~~marketing and~~ sales organization and have no experience as a company in commercializing products, and we may have to invest significant resources to develop these capabilities. If we are unable to establish ~~marketing and~~ sales capabilities or enter into agreements with third parties to market and sell our products, we may not be able to generate product revenue. We have no internal sales ~~, marketing~~ or distribution capabilities, nor have we commercialized a product. If any of our product candidates ultimately receives regulatory approval, we expect to establish a marketing and sales organization with technical expertise and supporting distribution capabilities to commercialize each such product in major markets, which will be expensive and time consuming. We have no prior experience as a company in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales ~~and marketing~~ personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales ~~, marketing~~ and distribution capabilities would adversely impact the commercialization of these products. We may also choose to collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. We may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. In addition, our product revenues and our profitability, if any, may be lower if we rely on third parties for these functions than if we were to market, sell and distribute any products that we develop ourselves. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we are not successful in commercializing our products, either on our own or through arrangements with one or more third parties, we may not be able to generate any future product revenue and we would incur significant additional losses **, which would have a material adverse effect on our results of operations and the trading price of our common stock** . Our future growth may depend, in part, on our ability to operate in foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties. Our future growth may depend, in part, on our ability to develop and commercialize our product candidates in foreign markets. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from applicable regulatory authorities in foreign markets, and we may never receive such regulatory approvals for any of our product candidates. To obtain separate regulatory approval in many other countries we must comply with numerous and varying regulatory requirements regarding safety and efficacy and governing, among other things, clinical trials, commercial sales, pricing and distribution of our product candidates. **Obtaining and maintaining marketing approval of our current and future product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain marketing approval in any other jurisdiction, while a failure or delay in obtaining marketing approval in one jurisdiction may have a negative effect on the marketing approval process in others.** If we obtain regulatory approval of our product candidates and ultimately commercialize our products in foreign markets, we would be subject to additional risks and uncertainties **, any of which could result in a material adverse effect on our business, prospectus and results of operations** , including: • different regulatory requirements for approval of drugs in foreign countries; • reduced protection for intellectual property rights; • the existence of additional third- party patent rights of potential relevance to our business; • unexpected changes in tariffs, trade barriers and regulatory requirements; • economic weakness, including inflation, or political instability in **domestic and** particular foreign economies and markets; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; • foreign reimbursement, pricing and insurance regimes; • workforce uncertainty in countries where labor unrest is common; • production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and • business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires. Risks related to our business operations and..... or earnings guidance we may provide. Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management, particularly our Chief Executive Officer, as well as our senior scientists and other members of our senior management team. The loss of services of any of these individuals could delay or prevent the successful development of our product pipeline, initiation or completion of our planned clinical trials or the commercialization of our product candidates. Although we have executed employment agreements or offer letters with each member of our senior management team, these agreements are terminable at will with or without notice ~~and~~ , **and** therefore, we may not be able to retain their services as expected. We do not currently maintain " key person " life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not have adequate compensation for the loss of the services of these individuals. We will need to expand and effectively manage our managerial,

operational, financial and other resources in order to successfully pursue our clinical development and commercialization efforts. We may not be successful in maintaining our unique company culture and continuing to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among pharmaceutical, biotechnology and other businesses, particularly in the San Diego area. Our industry has experienced a high rate of turnover of management personnel in recent years **, and many of the companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do** . If we are not able to attract, integrate, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy. We may encounter difficulties in managing our growth and expanding our operations successfully. As of February ~~24~~ **20** , ~~2023~~ **2024** , we had ~~210~~ **290** full- time employees. As we continue development and pursue the potential commercialization of our product candidates, as well as function as a public company, we will need to expand our financial, development, regulatory, manufacturing **, operational** , marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Our future financial performance and our ability to develop and commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively **, which would have a material adverse effect on our business** . We conduct certain research and development operations through our Australian wholly- owned subsidiary. If we lose our ability to operate in Australia, or if our subsidiary is unable to receive the research and development tax credit allowed by Australian regulations, our business and results of operations could suffer. In January 2017, we formed a wholly- owned Australian subsidiary, CAPL, to conduct various preclinical and clinical activities for our product and development candidates in Australia. Due to the geographical distance and lack of employees currently in Australia, as well as our lack of experience operating in Australia, we may not be able to efficiently or successfully monitor, develop and commercialize our lead products in Australia, including conducting clinical trials. Furthermore, we have no assurance that the results of any clinical trials that we conduct for our product candidates in Australia will be accepted by the FDA or foreign regulatory authorities for development and commercialization approvals. In addition, current Australian tax regulations provide for a refundable research and development tax credit equal to 43. 5 % of qualified expenditures. If we lose our ability to operate CAPL in Australia, or if we are ineligible or unable to receive the research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, our business and results of operation may be adversely affected. We are subject to various foreign, federal and state healthcare laws and regulations, and our failure to comply with these laws and regulations could harm our results of operations and financial condition. Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third- party payors and customers expose us to broadly applicable federal and state fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any products for which we obtain marketing approval. Such laws include: • the federal Anti- Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or providing any remuneration (including any kickback, bribe or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, in return for, either the referral of an individual or the purchase, lease, or order, or arranging for or recommending the purchase, lease, or order of any good, facility, item or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the federal statute or specific intent to violate it in order to have committed a violation; • the federal false claims, including the civil False Claims Act, which, among other things, impose criminal and civil penalties against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making or causing to be made a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act; • HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or 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. Similar to the federal Anti- Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. • the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program (with certain exceptions) to report annually to the government information related to payments and other " transfers of value " made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain other healthcare professionals (physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists, anesthesiology assistants and certified nurse midwives), and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members; and • analogous state and foreign laws and regulations, such as state anti- kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers, or by the patients themselves; state laws that require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and

regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to physicians, other healthcare providers and entities; state and local laws that require the registration of pharmaceutical sales representatives. Ensuring that our internal operations and business arrangements with third parties comply with applicable healthcare laws and regulations could involve substantial costs. It is possible that governmental authorities will conclude that our business practices, including our consulting and advisory board arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, do not comply with current or future statutes, regulations, agency guidance 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 the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from U. S. government funded healthcare programs, such as Medicare and Medicaid, or similar programs in other countries or jurisdictions, disgorgement, individual imprisonment, contractual damages, reputational harm, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, diminished profits and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly, time- consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. If any of the physicians or other providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusion from government funded healthcare programs and imprisonment. If any of the above occur, it could adversely affect our ability to operate our business and our results of operations. Actual or perceived failures to comply with applicable data protection, privacy and security laws, regulations, standards and other requirements could have a material adverse effect on our business, financial condition or results of operations. Privacy and data security have become significant issues in the U. S., E. U. and in many other jurisdictions where we may in the future conduct our operations. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing focus on privacy and data protection issues, which may affect our business and may increase our compliance costs and exposure to liability. As we receive, collect, process, use and store personal and confidential data, we are or may be subject to diverse laws and regulations relating to data privacy and security. Compliance with these privacy and data security requirements is rigorous and time- intensive and may increase our cost of doing business, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation and reputational harm, which could materially and adversely affect our business, financial condition and results of operations. In the U. S., we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their implementing regulations, or collectively, HIPAA, impose, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information held by covered entities and their business associates. We may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Depending on the facts and circumstances, we could be subject to criminal penalties if we knowingly receive individually identifiable health information from a HIPAA- covered entity in a manner that is not authorized or permitted by HIPAA. In addition, state laws govern the privacy and security of health- related and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts. By way of example, California enacted the California Consumer Privacy Act, or CCPA, effective January 1, 2020, which gives California residents expanded rights to access **, correct,** and delete their personal information, opt out of certain personal information sharing **and disclosure** , and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risks associated with, data breach litigation. The CCPA may increase our compliance costs and potential liability. Further, the California Privacy Rights Act, or CPRA, generally went into effect on January 1, 2023, and significantly amends the CCPA. The CPRA imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement, and additional compliance investment and potential business process changes may be required. Similar laws have passed in **Colorado, Connecticut, Delaware, Indiana, Iowa, Montana, Oregon, Tennessee, Texas, Utah, and** Virginia ~~, Connecticut, Utah and Colorado~~ , and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States **. Further states have also enacted consumer health date privacy laws, including states without comprehensive consumer privacy laws, such as Nevada and Washington state** . The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition. In the European Economic Area, or EEA, the General Data Protection Regulation, or GDPR, imposes stringent requirements for controllers and processors of personal data, including, for example, high standards for obtaining consent from individuals to process their personal data, robust disclosures to individuals and a strong individual data rights regime, short timelines for data breach notifications, limitations on retention and secondary use of information, significant requirements pertaining to health data and pseudonymized (i. e., key- coded) data and obligations when we contract third- party processors in connection with the processing of the personal data. Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to € 20 million or 4 % of the annual global revenues of

the noncompliant company, whichever is greater. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU- US Privacy Shield Framework, or Privacy Shield, under which personal data could be transferred from the EEA to US entities who had self-certified under the Privacy Shield scheme and imposed further restrictions on the use of standard contractual clauses, or SCCs. In March 2022, the US and EU announced a new regulatory regime intended to replace the invalidated regulations **with the Trans** ~~; however, this new EU-~~ ~~US~~ **Atlantic** Data Privacy Framework ~~has not been implemented beyond~~ **, or EU- U. S. DPF. In July 2023, the European Commission adopted** an **adequacy** ~~executive order signed by President Biden on October 7, 2022 on Enhancing Safeguards for United States Signals Intelligence Activities. European court and regulatory decisions subsequent to the CJEU~~ decision **in relation** ~~of July 16, 2020 have taken a restrictive approach~~ to ~~international~~ **the EU- U. S. DPF, allowing the EU- U. S. DPF to be utilized as a means of legitimizing EU- U. S. personal** data transfers **for participating entities. The EU- U. S. DPF may be subject to legal challenges from privacy advocacy groups or others, and the European Commission' s adequacy decision regarding the EU- U. S. DPF provides that the EU- U. S. DPF will be subject to future reviews and may be subject to suspension, amendment, repeal, or limitations to its scope by the European Commission** . As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and / or start taking enforcement action, we could suffer additional costs, complaints and / or regulatory investigations or fines, and / or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. Additionally, from 1 January 2021, we have been subject to the GDPR and also the UK GDPR which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, e. g. fines up to the greater of € 20 million (£ 17. 5 million) or 4 % of global turnover. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business. Compliance with U. S. and foreign data privacy and security laws, rules and regulations could require us to take on more onerous obligations in our contracts, require us to engage in costly compliance exercises, restrict our ability to collect, use and disclose data, or in some cases, impact our or our partners' or suppliers' ability to operate in certain jurisdictions. Each of these constantly evolving laws can be subject to varying interpretations. If we fail to comply with any such laws, rules or regulations, we may face government investigations and / or enforcement actions, fines, civil or criminal penalties, private litigation or adverse publicity that could adversely affect our business, financial condition and results of operations. Recently enacted legislation, future legislation and healthcare reform measures may increase the difficulty and cost for us to obtain marketing approval for and commercialize our product candidates and may affect the prices we may set. In the United States and some foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system, including cost- containment measures that may reduce or limit coverage and reimbursement for newly approved drugs and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In particular, there have been and continue to be a number of initiatives at the U. S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010, the ACA was enacted in the United States. Among the provisions of the ACA of importance to our potential product candidates, the ACA: established an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; expanded eligibility criteria for Medicaid programs; increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program; created a new Medicare Part D coverage gap discount program; established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare Innovation at the Centers for Medicare and Medicaid Services to test innovative payment and service delivery models to lower Medicare and Medicaid spending. Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U. S. Supreme Court dismissed the most recent judicial challenge to the ACA without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court' s decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. **It is unclear how any such challenges and the healthcare reform measures of the Biden administration, or any future presidential administration, will impact the ACA or our business.** In addition, other legislative changes have been proposed and adopted since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, included reductions to Medicare payments to providers, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2032 ~~, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022~~ , unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In addition, on March 11, 2021, the American Rescue Plan Act of 2021 was signed into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100 % of a drug' s average manufacturer price, or AMP, beginning January 1, 2024. Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation

designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. On August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. **On June 30, 2023 the Centers for Medicare and Medicaid Services, or CMS, issued new guidance detailing the requirements and parameters of the first round of price negotiations, to take place during 2023 and 2024, for products subject to the " maximum fair price " provision that would become effective in 2026. 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. CMS and HHS will continue to issue and update guidance as these programs are implemented.** For that and other reasons, it is currently unclear how the IRA will be effectuated. At the state level, individual states in the United States are also increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including **prescription drug affordability boards,** price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third- party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates, if approved, or put pressure on our product pricing, which could negatively affect our business, results of operations, financial condition and prospects. We expect that these new laws and other healthcare reform measures that may be adopted in the future may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates, if approved **, which could have a material adverse effect on our results of operations and financial condition** . If product liability **or state consumer protection act** lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our products. We face an inherent risk of product liability as a result of the clinical trials of our product candidates and will face an even greater risk if we commercialize our product candidates. For example, we may be sued if our product candidates allegedly cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability and a breach of warranties. Claims may be brought against us by clinical trial participants, patients or others using, administering or selling products that may be approved in the future, ~~or~~ **and** could be asserted **as product liability claims or** under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or cease the commercialization of our products. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in: • decreased demand for our products; • injury to our reputation and significant negative media attention; • withdrawal of clinical trial participants **and potential termination of clinical trial sites or entire clinical programs** ; • costs to defend the related litigation; • a diversion of management' s time and our resources; • substantial monetary awards to trial participants or patients; • product recalls, withdrawals or labeling, marketing or promotional restrictions **; • initiation of investigations and enforcement actions by regulators** ; • significant negative financial impact; • the inability to commercialize our product candidates; and • a decline in our stock price. We currently hold $ 10 million in product liability insurance coverage in the aggregate. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our product candidates. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies will also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts **, which could have a material adverse effect on our business, results of operations and financial condition** . We and any of our potential future collaborators will be required to report to regulatory authorities if any of our approved products cause or contribute to adverse medical events, and any failure to do so would result in sanctions that would materially harm our business. If we and any of our potential future collaborators are successful in commercializing our products, the FDA and foreign regulatory authorities would require that we and any of our potential future collaborators report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We and any of our potential future collaborators or CROs may fail to report adverse events within the prescribed timeframe. If we or any of our potential future collaborators or CROs fail to comply with such reporting obligations, the FDA or

a foreign regulatory authority could take action, including **sanctions,** criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products **, which could have a material adverse effect on our business, results of operations and financial condition** . Our employees and independent contractors, including principal investigators, CROs, consultants **, commercial partners** and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements. We are exposed to the risk that our employees and independent contractors, including principal investigators, CROs, consultants **, commercial partners** and vendors may engage in misconduct or other **improper or** illegal activity. Misconduct by these parties could include intentional, reckless and / or negligent conduct or ~~disclosure of~~ unauthorized activities ~~to us~~ that violate: (1) the laws and regulations of the FDA and other **regulators and other** similar regulatory requirements, including those laws that require the reporting of true, complete and accurate information to such authorities, manufacturing standards, (2) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and abroad **,** or (3) laws that require the true, complete and accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials, or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation **. Sales, marketing and other business arrangements in the healthcare industry are also subject to extensive laws intended to prevent fraud, kickbacks, self- dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. In addition, during the course of our operations our directors, executives, and employees may have access to material, nonpublic information regarding our business, our results of operations, or potential transactions we are considering. We may not be able to prevent a director, executive, or employee from trading in our common stock on the basis of, or while having access to, material, nonpublic information** . It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. We may engage in strategic transactions that could impact..... financial condition and prospects. We may not realize any benefits from our relationship with Radionetics. **We no longer hold** ~~In conjunction with formation of Radionetics, we initially retained~~ a majority equity stake in Radionetics **,** and **we do not control** ~~have the potential to receive future sales milestones and royalties on net sales of~~ any ~~approved products subject and pursuant to the terms~~ of ~~our license agreement~~ **its key activities** . ~~However~~ **Further** , Radionetics will **continue to** need additional capital to advance its pipeline **,** and our ownership interest may be ~~diminished~~ **further diluted** in connection with future capital raising. In addition, our ability to receive milestone or royalty payments from Radionetics **subject and pursuant to the terms of the Radionetics License** will depend on Radionetics **'** ability to advance its pipeline through clinical development, regulatory approval and ultimately commercial sales, all of which will take significant time, will be subject to inherent risks in drug development and may be impacted by changes in regulatory requirements, healthcare reform measures and competitive dynamics. Further, the Radionetics nonpeptide therapeutics platform technology targeting the delivery of therapeutic radioisotopes is novel and unproven and may never lead to approved products of commercial value. As a result, we ~~and our stockholders~~ may never realize future value from our equity interest in ~~or~~ **Radionetics, the Radionetics** ~~license~~ **License** ~~agreement~~ or research collaboration with Radionetics **, which could have a material adverse effect on our financial condition and the trading price of our common stock. The increasing use of social media platforms presents new risks and challenges. Social media is increasingly being used to communicate about our product candidates, technologies and programs, and the diseases our product candidates are designed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media channels to comment on the effectiveness of a product candidate or to report an alleged adverse event. When such disclosures occur, there is a risk that we fail to monitor and comply with applicable adverse event reporting obligations or we may not be able to defend ourselves or the public' s legitimate interests in the face of the political and market pressures generated by social media due to restrictions on what we may say about our product candidates. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face overly restrictive regulatory actions or incur other harm to our business** . Risks related to our intellectual property Our commercial success depends in part on our ability to obtain and maintain **intellectual property** ~~patent protection and trade secret~~ protection for our product candidates, proprietary technologies **,** and their uses **,** as well as our ability to operate without infringing ~~upon~~ the proprietary rights of others. We generally seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates, proprietary technologies and their uses that are important to our business. Our patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless, and until, patents issue from such

applications, and then only to the extent the issued claims cover the technology. There can be no assurance that our patent applications will result in patents being issued or that issued patents will afford sufficient protection against competitors with similar technology, nor can there be any assurance that the patents issued will not be infringed, designed around, or invalidated by third parties. Even issued patents may later be found invalid or unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. The degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. This failure to obtain ~~the~~ **effective** intellectual property rights relating to our product candidates could have a material adverse effect on our financial condition and results of operations. The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the scope of claims allowable in patents in the pharmaceutical and biotechnology space has emerged in the United States. The relevant patent laws and their interpretation outside of the United States is also uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our technology or product candidates and could affect the value of such intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell or importing products that infringe our intellectual property will depend in part on our success in obtaining and enforcing patent claims that cover our technology, inventions and improvements. We cannot guarantee that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications we may file in the future, nor can we be sure that any patents that may be granted to us in the future will be commercially useful in protecting our products, the methods of use or manufacture of those products. Moreover, even our issued patents do not guarantee us the right to practice our technology in relation to the commercialization of our products. Patent and other intellectual property rights in the pharmaceutical and biotechnology space are evolving and involve many risks and uncertainties. For example, third parties may have blocking patents that could be used to prevent us from commercializing our product candidates and practicing our proprietary technology, and our issued patents may be challenged, invalidated or circumvented, which could limit our ability to stop competitors from marketing related products or could limit the term of patent protection that otherwise may exist for our product candidates. In addition, the scope of the rights granted under any issued patents may not provide us with protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies that are outside the scope of the rights granted under any issued patents. For these reasons, we may face competition with respect to our product candidates **even if our patent applications are granted** . Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any particular product candidate can be commercialized, any patent protection for such product may expire or remain in force for only a short period following commercialization, thereby reducing the commercial advantage the patent provides. The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our potential future collaborators will be successful in protecting our product candidates by obtaining and defending patents. These risks and uncertainties include but are not limited to the following: • the USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process, the noncompliance with which can result in abandonment or lapse of a patent or patent application, and partial or complete loss of patent rights in the relevant jurisdiction; • patent applications may not result in any patents being issued; • patents may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage; • our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with or eliminate our ability to make, use and sell our potential product candidates; • there may be significant pressure on the U. S. government **, other governmental authorities,** and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and • countries other than the United States may have patent laws less favorable to patentees than those upheld by U. S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates. The patent prosecution process is also expensive and time- consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions where protection may be commercially advantageous. 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. **although we** enter into non- disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output,such as our employees,outside scientific collaborators,CROs,third- party manufacturers ~~,suppliers,contractors~~ ,consultants,advisors and other third parties,any of these parties may breach such agreements and disclose such output before a patent application is filed,thereby jeopardizing our ability to seek patent protection.Given the amount of time required for the development,testing and regulatory review of new product candidates,patents protecting such candidates might expire before or shortly after such candidates are commercialized.As a result,our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours ~~,which could have a material adverse effect on our business and prospects~~ .If the scope of any patent protection we obtain is not sufficiently broad,or if we lose any of our patent protection,our ability to prevent our competitors from commercializing similar or identical product candidates would be ~~material and~~ adversely affected.The patent position of biopharmaceutical companies is generally highly uncertain,involves complex legal and factual questions,and has been the subject of much litigation in recent years.As a result,the issuance,scope,validity,enforceability and commercial value of our patent rights are highly uncertain.Our pending and future patent applications may not result in patents being issued which protect our product candidates or which effectively prevent others from commercializing competitive product candidates.Moreover,the coverage claimed in a patent application can be significantly reduced before the patent is issued,and its scope can be reinterpreted after issuance.Even if patent applications we own currently or in the future issue as

patents,they may not issue in a form that will provide us with any meaningful protection,prevent competitors or other third parties from competing with us,or otherwise provide us with any competitive advantage.Any issued patents that we own may be challenged or circumvented by third parties or may be narrowed or invalidated as a result of challenges by third parties.Consequently,we do not know whether our product candidates will be protectable or remain protected by valid and enforceable patents.Our competitors or other third parties may be able to **circumvent our patents by developing similar or alternative technologies or products in a non- infringing manner** The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability. Our patents may be challenged in the courts or patent offices in the United States and abroad ~~,~~and may be narrowed or invalidated as a result of challenges by third parties. We may be subject to a third- party pre- issuance submission of prior art to the USPTO, or become involved in opposition, derivation, revocation, reexamination, post- grant review, or PGR, and inter partes review, or IPR, or other similar proceedings challenging our owned patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third- party patent rights. Moreover, our patents may become subject to post- grant challenge proceedings, such as oppositions in a foreign patent office, ~~that~~ **which** challenge our priority of invention or other features of patentability with respect to our patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity or patent claims being narrowed, invalidated ~~,~~or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products ~~to ours~~ , or limit the duration of the patent protection of our product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. In addition, if the breadth or strength of protection provided by our ~~issued~~ patents and ~~pending~~ patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates ~~. In addition~~ , although we enter into non- disclosure..... products in a non- infringing manner which could **have a** ~~materially~~ -- **material** ~~adversely~~ -- **adverse** ~~affect~~ **effect on** our business ~~, financial condition, results of operations~~ and prospects ~~. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third- party pre- issuance submission of prior art to the USPTO, or become involved in opposition, derivation, revocation, reexamination, post- grant review, or PGR, and inter partes review, or IPR, or other similar proceedings challenging our owned patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third- party patent rights. Moreover, our patents may become subject to post- grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our priority of invention or other features of patentability with respect to our patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity or patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates~~ . Some of our intellectual property has been discovered through government funded programs and thus may be subject to federal regulations such as " march- in " rights, certain reporting requirements and a preference for U. S.- based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non- U. S. manufacturers. ~~Most~~ **Some** of our intellectual property rights, including those ~~for~~ **covering the compounds in** our lead programs **(paltusotine and CRN04894)** , have been generated through the use of U. S. government funding provided from SBIR Grants awarded to us prior to 2020 by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, and are therefore subject to certain federal regulations. As a result, the U. S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh- Dole Act of 1980, or Bayh- Dole Act. These U. S. government rights include a non- exclusive, non- transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U. S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non- exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as " march- in rights "). The U. S. government also has the right to take title to these inventions if we fail to disclose the invention to the government or fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U. S. government requires that any products embodying any of these inventions or produced through the use of any of these inventions be manufactured substantially in the United States. This preference for U. S. industry may be waived by the federal agency that provided the funding if the owner or assignee of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U. S. industry may limit our ability to contract with non- U. S. product manufacturers for products covered by such intellectual property. To the extent any of our future intellectual property is also generated through the use of U. S. government funding, the provisions of the Bayh- Dole Act may similarly apply. We may be involved in lawsuits to protect or enforce our patents, which

could be expensive, time consuming and unsuccessful. Further, our issued patents could be found invalid or unenforceable if challenged in court. Competitors may infringe our intellectual property rights. To prevent infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time- consuming. In addition, in a patent infringement proceeding, a court may decide that a patent we own is not valid, is unenforceable and / or is not infringed. If we or any of our potential future collaborators were to initiate legal proceedings against a third party to enforce a patent directed at one of our product candidates, the defendant could counterclaim that our patent is invalid and / or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and / or unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including but not limited to lack of novelty, obviousness, written description or non- enablement. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. Third parties may also raise similar invalidity claims before the USPTO or patent offices abroad, even outside the context of litigation. Such mechanisms include re- examination, PGR, IPR, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e. g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of or amendment to our patents in such a way that they no longer cover our technology or platform, or any product candidates that we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. ~~If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our technology or platform, or any product candidates that we may develop. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations and prospects. The outcome following legal assertions of invalidity and / or unenforceability is unpredictable, and prior art could render our patents invalid. There is no assurance that all potentially relevant prior art relating to our issued patents and pending patent applications has been found.~~ There is also no assurance that there is not prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim in our patents and patent applications, which may, nonetheless, ultimately be found to affect the validity or enforceability of a patent claim. If a ~~defendant~~ **third party** were to prevail on a legal assertion of invalidity ~~and /~~ or unenforceability, we would lose at least part, and perhaps all, of the patent protection ~~for such~~ **on our** product ~~candidate~~ **candidates** ~~(s)~~ **or other intellectual property that we may develop** . In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such a loss of patent protection would have a material adverse impact on our business **, financial condition, results of operations and prospects** . Even if resolved in our favor, litigation or other legal proceedings relating to our intellectual property rights may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities ~~. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace~~ . Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other legal proceedings relating to our intellectual property rights, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or other proceedings. **In addition,** ~~There~~ **there** could ~~also~~ be public announcements of the results of hearings, motions or other interim proceedings or developments ~~. If~~ **and if** securities analysts or investors perceive these results to be negative, it could have a ~~material~~ **substantial** adverse effect on the price of our common stock. ~~In addition~~ **Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales , marketing or distribution activities. We may not have sufficient financial or** ~~the~~ **other** ~~issuance~~ **resources to conduct such litigation or proceedings adequately. Some** of ~~a~~ **our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of** patent **litigation or** ~~does not give us the~~ **other proceedings** ~~right to practice the patented invention. Third parties may have blocking patents that~~ could **compromise** ~~prevent us from marketing~~ our **ability to compete in the marketplace** ~~own patented product and practicing our own patented technology~~ . Intellectual property rights do not necessarily address all potential threats to our competitive advantage. The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example: • others may be able to develop products that are similar to our product candidates but that are not covered by the claims of the patents that we own; • we might not have been the first to make the inventions covered by the issued patents or patent application that we own; • we might not have been the first to file patent applications covering certain of our inventions; • others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights; • it is possible that our pending patent applications will not lead to issued patents; • issued patents that we own may be held invalid or unenforceable, as a result of legal challenges by our competitors; • our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets; • we may not develop additional proprietary technologies that are patentable; and • the patents of others may have an adverse effect on our business. Should any of these events occur, it could

significantly harm our business, results of operations and prospects. Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties. Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts. Our commercial success depends in part on avoiding infringement of the patents and proprietary rights of third parties. However, our research, development and commercialization activities may be subject to claims that we infringe or otherwise violate patents or other intellectual property rights owned or controlled by third parties. Other entities may have or obtain patents or proprietary rights that could limit our ability to make, use, sell, offer for sale or import our product candidates and products that may be approved in the future, or impair our competitive position. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biopharmaceutical industry, including patent infringement lawsuits, oppositions, reexaminations, IPR proceedings and PGR proceedings before the USPTO and / or corresponding foreign patent offices. Numerous third- party U. S. and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates. There may be third- party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. As the biopharmaceutical industry expands and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties. Because patent applications are maintained as confidential for a certain period of time, until the relevant application is published, we may be unaware of third-party patents that may be infringed by commercialization of any of our product candidates, and we cannot be certain that we were the first to file a patent application related to a product candidate or technology. Moreover, because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, identification of third- party patent rights that may be relevant to our technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. There is also no assurance that there is not prior art of which we are aware, but which we do not believe is relevant to our business, which may, nonetheless, ultimately be found to limit our ability to make, use, sell, offer for sale or import our products that may be approved in the future, or impair our competitive position. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Any claims of patent infringement asserted by third parties would be time consuming and could: • result in costly litigation that may cause negative publicity; • divert the time and attention of our technical personnel and management; • cause development delays; • prevent us from commercializing any of our product candidates until the asserted patent expires or is held finally invalid or not infringed in a court of law; • require us to develop non- infringing technology, which may not be possible on a cost- effective basis; • subject us to significant liability to third parties; or • require us to enter into royalty or licensing agreements, which may not be available on commercially reasonable terms, or at all, or which might be non- exclusive, which could result in our competitors gaining access to the same technology. Although no third party has asserted a claim of patent infringement against us as of the date of this Annual Report on Form 10- K, others may hold proprietary rights that could prevent our product candidates from being marketed **once approved** . Any patent- related legal action against us claiming damages and seeking to enjoin commercial activities relating to our products or processes could subject us to potential liability for damages, including treble damages if we were determined to willfully infringe, and require us to obtain a license to manufacture or market our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. Moreover, even if we or our future strategic partners were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. In addition, we cannot be certain that we could redesign our product candidates or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could **delay or** prevent us from developing and commercializing our product candidates, which could harm our business, financial condition and operating results. In addition, intellectual property litigation, regardless of its outcome, may cause negative publicity and could prohibit us from marketing or otherwise commercializing our product candidates and technology. Parties making claims against us may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have material adverse effect on our ability to raise additional funds or otherwise have a material adverse effect on our business, results of operations, financial condition and prospects. Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our common shares to decline. During the course of any intellectual property litigation, there could be public announcements of the initiation of the litigation as well as results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our existing products, programs or intellectual property could be diminished. Accordingly, the market price of shares of our common stock may decline. Such announcements could also harm our reputation or the market for our future products, which could have a material adverse effect on our business. Derivation proceedings may be necessary to determine priority of inventions, and an unfavorable outcome may require us to cease using the related technology or to attempt to license rights from the prevailing party. Derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of derivation proceedings may

fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with such proceedings could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties or enter into development or manufacturing partnerships that would help us bring our product candidates to market. Changes in U. S. patent law, or laws in other countries **or jurisdictions** , could diminish the value of patents in general, thereby impairing our ability to protect our product candidates. As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involve a high degree of technological and legal complexity. Therefore, obtaining and enforcing pharmaceutical patents is costly, time consuming and inherently uncertain. Changes in either the patent laws or in the interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property and may increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. We cannot predict the breadth of claims that may be allowed or enforced in our patents or in third- party patents. In addition, Congress or other foreign legislative bodies may pass patent reform legislation that is unfavorable to us. For example, the U. S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U. S. Congress, the U. S. federal courts, the USPTO, or similar authorities in foreign jurisdictions, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents we might obtain in the future. We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property. We may also be subject to claims that former employees or other third parties have an ownership interest in our patents or other intellectual property. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and distraction to management and other employees. Patent terms may be inadequate to protect our competitive position on our product 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 product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. If we do not obtain patent term extension for our product candidates, our business may be materially harmed. Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one or more of our U. S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch- Waxman Amendments. The Hatch- Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. A maximum of one patent may be extended per FDA approved product as compensation for the patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only those claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended. Patent term extension may also be available in certain foreign countries upon regulatory approval of our product candidates. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. We may not be able to protect our intellectual property rights throughout the world. Patents are of national or regional effect. Filing, prosecuting and defending patents in all countries throughout the world could 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. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of many foreign countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights. As an example, **as of June 2023,** European **patent** applications ~~will soon~~ have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court, or UPC **. Patents**

granted before the implementation of the UPC will have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC may be potentially vulnerable to a single UPC- based revocation challenge that, if successful, could invalidate the patent in all countries who ratified the Unitary Patent Court Agreement . The option of a Unitary Patent will be a significant change in European patent practice. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected. Further, the standards applied by the USPTO and foreign patent offices in granting patents are not always applied uniformly or predictably. As such, we do not know the degree of future protection that we will have on our product candidates, proprietary technologies, and their uses. While we will endeavor to try to protect our product candidates, proprietary technologies, and their uses, with intellectual property rights such as patents, as appropriate, the process of obtaining patents is time consuming, expensive, and unpredictable. Further, geo-political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors. For example, the United States and foreign government actions related to Russia' s invasion of Ukraine may limit or prevent filing, prosecution, and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees that have citizenship or nationality in, are registered in, or have predominately primary place of business or profit-making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected. Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by regulations and 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 the USPTO and various foreign patent offices at various points over the lifetime of our patents and / or applications. We have systems in place to remind us to pay these fees, and we rely on our outside patent annuity service to pay these fees when due. Additionally, the USPTO and various foreign patent offices, require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with rules applicable to the particular jurisdiction. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If such an event were to occur, it could have a material adverse effect on our business. If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected. Even though we have filed ~~three~~ **multiple** trademark registration applications in the ~~USPTO~~ **United States, as well as jurisdictions outside the United States** , we cannot be certain that our registered or unregistered U. S. trademarks or trade names, or the corresponding trademarks or trade names registered in foreign territories, will not be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our financial condition or results of operations. If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed. In addition, we rely on the protection of our trade secrets, including unpatented know- how, technology and other proprietary information to maintain our competitive position. Although we have taken steps to protect our trade secrets and unpatented know- how, including entering into confidentiality agreements with third parties, and confidential information and inventions agreements with employees, consultants and advisors, we cannot provide any assurances that all such agreements have been duly executed, and any of these

parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time- consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. Moreover, third parties may still obtain this information or may come upon this or similar information independently, and we would have no right to prevent them from using that technology or information to compete with us. If any of these events occurs or if we otherwise lose protection for our trade secrets, the value of this information may be greatly reduced, and our competitive position would be harmed. If we do not apply for patent protection prior to such publication or if we cannot otherwise maintain the confidentiality of our proprietary technology and other confidential information, then our ability to obtain patent protection or to protect our trade secret information may be jeopardized. We may be subject to claims that we have wrongfully hired an employee from a competitor or that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets of their former employers. As is common in the pharmaceutical industry, in addition to our employees, we engage the services of consultants to assist us in the development of our product candidates. Many of these consultants, and many of our employees, were previously employed at, or may have previously provided or may be currently providing consulting services to, other pharmaceutical companies including our competitors or potential competitors. We may become subject to claims that we, our employees or a consultant inadvertently or otherwise used or disclosed trade secrets or other information proprietary to their former employers or their former or current clients. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely affect our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team and other employees. Risks related to our common stock An active, liquid and orderly market for our common stock may not be maintained. Our common stock began trading on the Nasdaq Global Select Market, or Nasdaq, in 2018, and we can provide no assurance that we will be able to maintain an active trading market for our common stock. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. An inactive market may also impair our ability to raise capital by selling shares and may impair our ability to acquire other businesses or technologies using our shares as consideration, which, in turn, could materially adversely affect our business. Our stock price has been and is likely to be volatile. The stock market in general and the market for stock of pharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their common stock at or above the price at which they paid. The market price for our common stock may be influenced by those factors discussed in this " Risk Factors " section and many others, including: • our ability to enroll subjects in our ongoing and planned clinical trials; • results of our clinical trials and preclinical studies, and the results of trials of our competitors or those of other companies in our market sector; • **failure to meet or exceed drug development or financial projections we provide to the public or of the investment community; •** regulatory approval of our product candidates, or limitations to specific label indications or patient populations for its use, or changes or delays in the regulatory review process; • regulatory **or legal** developments in the United States and foreign countries; • changes in the structure of healthcare payment systems, especially in light of current reforms to the U. S. healthcare system; • the success or failure of our efforts to acquire, license or develop additional product candidates; • innovations or new products developed by us or our competitors; • announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments; • manufacturing, supply or distribution delays or shortages; • any changes to our relationship with any manufacturers, suppliers, future collaborators or other strategic partners; • achievement of expected product sales and profitability; • variations in our financial results or those of companies that are perceived to be similar to us; • market conditions in the pharmaceutical sector and issuance of securities analysts' reports or recommendations; • trading volume of our common stock; • an inability to obtain additional funding; • sales of our stock by **us,** insiders and stockholders **; • changes in accounting principles** ; • general economic, industry and market conditions or other events or factors, many of which are beyond our control, such as the ~~COVID- 19 pandemic~~ **impact of any natural disasters, including related to climate change, or public health emergencies** , inflation, interest rates **, actual or anticipated bank failures,** and ~~the~~ **international** military ~~conflict~~ **conflicts , including** between Russia and Ukraine **and in the Middle East** ; • additions or departures of key personnel; and • intellectual property, product liability or other litigation **by or** against us. In addition, in the past, stockholders have initiated class action lawsuits against pharmaceutical companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management' s attention and resources, which could have a material adverse effect on our business, financial condition and results of operations. Our ~~failure to meet the continued listing requirements of the Nasdaq Global Select Market could result in a delisting of our common stock. If we fail to satisfy the continued listing requirements of the Nasdaq Global Select Market, such as the corporate governance requirements or the minimum closing bid price requirement, Nasdaq may take steps to delist our common stock. Such a delisting would likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. In the event of a delisting, we can provide no assurance that any action taken by us to restore compliance with listing requirements would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below the Nasdaq minimum bid price requirement or prevent future non- compliance with Nasdaq' s listing requirements. Our~~ executive officers, directors and principal stockholders, if they choose to act together, have the ability to control or significantly influence all matters submitted to stockholders for approval. Our executive officers, directors and greater than 5 % stockholders, in the aggregate, own approximately ~~49~~ **26** . 7 % of our outstanding common stock as of February ~~24~~ **20** , ~~2023~~ **2024** . As a result, such persons, acting together, have the ability to control or significantly influence all matters submitted to our stockholders for approval, including the election and removal of directors and approval of any

significant transaction, as well as our management and business affairs. This concentration of ownership may have the effect of delaying, deferring or preventing a change in control, impeding a merger, consolidation, takeover or other business combination involving us, or discouraging a potential acquiror from making a tender offer or otherwise attempting to obtain control of our business, even if such a transaction would benefit other stockholders. We do not currently intend to pay dividends on our common stock, and, consequently, your ability to achieve a return on your investment will depend on appreciation, if any, in the price of our common stock. We have never declared ~~or~~ **nor** paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. In addition, the terms of any future debt agreements may preclude us from paying dividends. Any return to stockholders will therefore be limited to the appreciation of their stock. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which stockholders have purchased their shares. Sales of a substantial number of shares of our common stock by our existing stockholders in the public market could cause our stock price to fall. Sales of a substantial number of shares of our common stock **by our existing stockholders** in the public market or the perception that these sales might occur could significantly reduce the market price of our common stock and impair our ability to raise adequate capital through the sale of additional equity securities ~~. The holders of 5, 461, 446 shares of our outstanding common stock, or approximately 10. 1 % of our total outstanding common stock as of February 24, 2023, are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates, as defined in Rule 144 under the Securities Act. Sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock~~ . 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 could significantly reduce the value of our shares to a potential acquiror or delay or prevent changes in control or changes in our management without the consent of our board of directors. The provisions in our charter documents include the following: • 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; • no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates; • the exclusive right of our board of directors, unless the board of directors grants such right to the stockholders, 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; • the required approval of at least 66- 2 / 3 % of the shares entitled to vote to remove a director for cause, and the prohibition on removal of directors without cause; • the ability of our board of directors to authorize the issuance of shares of 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 acquiror; • the ability of our board of directors to alter our amended and restated bylaws without obtaining stockholder approval; • the required approval of at least 66- 2 / 3 % of the shares entitled to vote to adopt, amend or repeal our amended and restated bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors; • a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders; • an exclusive forum provision providing that the Court of Chancery of the State of Delaware will be the exclusive forum for certain actions and proceedings; • the requirement that a special meeting of stockholders may be called only by 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 • 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 acquiror from conducting a solicitation of proxies to elect the acquiror' 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. Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, and our amended and restated bylaws provide that the federal district courts shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees. Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine; provided, however, that this exclusive forum provision would not apply to suits brought to enforce any liability or duty created by the Securities Act or the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. Furthermore, our amended and restated bylaws also provide that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. These provisions may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find this provision in our amended and restated certificate of incorporation and amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which

could adversely affect our business and financial condition. Our ability to use net operating loss carryforwards and other tax attributes may be limited. We have incurred substantial losses during our history, do not expect to become profitable in the near future, and may never achieve profitability. To the extent that we continue to incur net operating losses for tax purposes, or NOLs, such NOLs will carry forward to offset future taxable income (subject to limitations), if any, until such NOLs expire (if subject to expiration). As of December 31, ~~2022~~ **2023**, we had federal, state and foreign NOL carryforwards of approximately $ ~~254~~ **311**. ~~5~~ **3** million, $ ~~218~~ **228**. ~~0~~ **6** million and $ 1. ~~3~~ **7** million, respectively. The federal NOL carryforwards generated in taxable years beginning after December 31, 2017 of $ ~~248~~ **305**. ~~1~~ **0** million will carry forward indefinitely, but can be used to offset only up to 80 % of taxable income in a given taxable year (which may require us to pay federal income taxes in future years despite generating federal NOL carryforwards in prior years), while those NOL carryforwards generated in taxable years beginning prior to January 1, 2018 begin expiring in 2035, unless previously utilized, but are not subject to the 80 % annual limitation on use. $ 0. ~~5~~ **8** million of the state loss carryforwards will carryforward indefinitely. The remaining state NOL carryforwards begin expiring in 2035, unless previously utilized. Our foreign NOL carryforwards do not expire. We also have federal and California research and development (R & D) credit carryforwards and federal Orphan Drug Credits totaling $ ~~8~~ **16**. ~~8~~ **3** million, $ ~~6~~ **9**. ~~1~~ **5** million, and $ ~~12~~ **20**. 5 million, respectively. The federal R & D credits begin to expire in 2030, unless previously utilized, while the state credits do not expire. The federal Orphan Drug credit carryforwards will begin to expire in 2040, unless previously utilized. Our NOL carryforwards and other tax attributes (including tax credit carryforwards) are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Moreover, in general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an " ownership change " is subject to limitations on its ability to utilize its pre- ownership change NOL carryforwards or tax credit carryforwards to offset future taxable income or income tax liabilities, respectively. For these purposes, an ownership change generally occurs where the aggregate change in stock ownership of one or more stockholders or groups of stockholders owning at least 5 % of a corporation' s stock exceeds 50 percentage points over a rolling three- year period. Similar rules may apply under state or foreign tax laws. During 2020, we completed a study to assess whether any ownership changes within the meaning of Section 382 of the Code had occurred with respect to us for the time period prior to July 15, 2020. The study identified ownership changes during the fourth quarter of 2015, the first quarter of 2018 and the second quarter of 2020. We updated the study for 2022 and did not identify any additional ownership changes. These ownership changes have subjected, and will continue to subject, our NOLs and tax credits to an annual limitation on their utilization. However, our NOLs and tax credits are not expected to expire unused assuming we have taxable income or income tax liabilities in future periods. Although we do not expect these limitations to constrain utilization of our NOLs or tax credits, such limitations could result in the expiration of our NOLs or tax credits before they can be utilized and, if we are profitable, our future cash flows could be adversely affected due to our increased tax liability. In addition, future changes in our stock ownership, many of which are outside of our control, could result in additional ownership changes and further annual limitations. We have recorded a full valuation allowance related to our NOL carryforwards and other deferred tax assets due to the uncertainty of the ultimate realization of the future benefits of those assets. General risk factors ~~/~~ **engage in strategic transactions that could impact** ~~or~~ **our** ~~transformative~~ **liquidity,increase our expenses and present significant distractions to our management.From time to time,we may consider strategic** transactions,such as acquisitions of companies,asset purchases and out- licensing or in- licensing of intellectual property,products or technologies.Additional potential transactions that we may consider in the future include a variety of business arrangements,including spin- offs,strategic partnerships,joint ventures,restructurings,divestitures,business combinations and investments.Any ~~such transaction could be material and could disrupt our business or change our business profile,focus or strategy significantly.Any~~ future transactions could increase our near and long- term expenditures,result in potentially dilutive issuances of our equity securities,including our common stock,or the incurrence of debt,contingent liabilities,amortization expenses or acquired in- process research and development expenses,any of which could affect our financial condition,liquidity and results of operations.Future ~~transactions~~ **acquisitions** may also require us to obtain additional financing,which may not be available on favorable terms or at all.These transactions may never be successful and may require significant time and attention of management.In addition,the integration of any business that we may acquire in the future may disrupt our existing business and may be a complex,risky and costly endeavor for which we may never realize the full benefits **of the acquisition** ~~and could delay our timelines or otherwise adversely affect our business~~ .Accordingly,although there can be no assurance that we will undertake or successfully complete any **additional** transactions of the nature described above,any additional transactions that we do complete could have a material adverse effect on our business,results of operations,financial condition and prospects. **We may** We and any of our third- party manufacturers and suppliers may use potent chemical agents and hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly. We and any of our third- party manufacturers or suppliers will use biological materials, potent chemical agents and may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety of the environment. Our operations and the operations of our third- party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. In the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended. Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees

resulting from the use of hazardous materials or other work- related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects. Our information technology systems, or those of any of our CROs, manufacturers, other contractors or consultants or potential future collaborators, may fail or suffer security breaches, which could result in a material disruption of our product development programs. We collect and maintain information in digital form that is necessary to conduct our business, and we are increasingly dependent on information technology systems ~~and~~ **,** infrastructure **, and data** to operate our business. In the ordinary course of our business, we collect, store **, process,** and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information of ~~customers~~ **third parties** and our employees and contractors. It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. Despite the implementation of security measures, our information technology systems and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to attack, interruption and damage from computer viruses and malware (e. g. ransomware), malicious code, cyberattacks, hacking, phishing attacks **, deep fakes** and other social engineering schemes, ~~employee~~ **attacks enhanced or facilitated by artificial intelligence,** theft **, misconduct** or misuse **by personnel or third parties** , human error, fraud, denial or degradation of service attacks **, credential harvesting, supply- chain attacks, technological malfunctions or failures, software bugs, data and information loss** , sophisticated nation- state and nation-state- supported actors or unauthorized access or use by persons inside our organization, or persons with access to systems inside our organization. Attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. **We** ~~As a result of the COVID- 19 pandemic, we~~ may also face increased cybersecurity risks due to our reliance on internet technology and the number of our ~~employees~~ **personnel** who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence. We and certain of our service providers are from time to time subject to cyberattacks and security incidents **, including several of the types of attacks noted above** . While we ~~do~~ **have** not ~~believe that we have~~ experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. We also rely on third parties to manufacture our product candidates, and similar events relating to their computer systems could also have a material adverse effect on our business. 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 and the further development and commercialization of our product candidates could be delayed. If a disruption or security breach were to result in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential or proprietary or personal information, we could also incur liability, including litigation exposure, penalties and fines ~~, and we could become the subject of regulatory action or investigation~~ . Furthermore, federal, state and international laws and regulations can expose us to enforcement actions and investigations by regulatory authorities, and potentially result in regulatory penalties, fines and significant legal liability, if our information technology security efforts fail **. The cyber threat landscape is continually changing, and we cannot guarantee that we will be able to adapt and change our cyber program to manage and mitigate associated risks** . We maintain cyber liability insurance; however, this insurance may not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems. ~~Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.~~ Our operations could be subject to terrorism, war, earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, ~~medical~~ **health** epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self- insured. We rely on third- party **suppliers and** manufacturers to produce our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers **and manufacturers** were affected by a man- made or natural disaster or other business interruption **, which could have a material adverse effect on our business. For example, the COVID- 19 pandemic and government measures taken in response had a significant impact, both direct and indirect, on businesses and commerce, resulting in delays and interruptions in our drug manufacturing, nonclinical activities, clinical trials, review and approval timelines, and our discovery and development pipeline. A resurgence or the widespread occurrence of another deadly illness could adversely affect our business, operations and financial results** . In addition, our corporate headquarters is located in San Diego, California near major earthquake faults and fire zones, and the ultimate impact on us of being located near major earthquake faults and fire zones and being consolidated in a certain geographical area is unknown. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. Unfavorable global economic conditions could adversely affect our business, financial

condition and stock price. The global credit and financial markets are currently, and have from time to time, experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation **rates, fluctuations in currency exchange** rates, declines in consumer confidence, declines in economic growth, supply chain shortages, increases in unemployment rates and uncertainty about economic stability. For example, the Federal Reserve recently raised interest rates multiple times in response to concerns about inflation and it may raise them again. Higher interest rates, coupled with reduced government spending and volatility in financial markets may increase economic uncertainty and affect consumer spending. Increased inflation rates can adversely affect us by increasing our costs, including labor and employee benefit costs. The financial markets and the global economy may also be adversely affected by the current or anticipated impact of military conflict, including the ongoing conflict between Russia and Ukraine, **the Israel- Hamas war, impact of a potential U. S. government shutdown,** terrorism or other geopolitical events, with the potential to result in extreme volatility in the global capital markets and further global economic consequences, including disruptions of the global supply chain and energy markets. Sanctions imposed by the United States and other countries in response to such conflicts, including the one in Ukraine, may also adversely impact the financial markets and the global economy, and any economic countermeasures by the affected countries or others could exacerbate market and economic instability **. The closures of Silicon Valley Bank, or SVB, Signature Bank and First Republic Bank and their placement into receivership with the Federal Deposit Insurance Corporation, or FDIC, created bank- specific and broader financial institution liquidity risk and concerns. Although the Department of the Treasury, the Federal Reserve, and the FDIC jointly released a statement that depositors at SVB and Signature Bank would have access to their funds, even those in excess of the standard FDIC insurance limits, under a systemic risk exception, future adverse developments with respect to specific financial institutions or the broader financial services industry may lead to market- wide liquidity shortages, impair the ability of companies to access near- term working capital needs, and create additional market and economic uncertainty** . There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. **A future recession or market correction or other significant geopolitical events could materially affect our business and the value of our common stock.** Our general business strategy may be adversely affected by any such economic downturn, **liquidity shortages,** volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, including as a result of political unrest or war, **or if adverse developments are experienced by financial institutions,** it may **cause short- term liquidity risk and also** make any necessary debt or equity financing more difficult, more costly **, more onerous with respect to financial and operating covenants** and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may ~~not survive an economic downturn~~ **be adversely affected by the foregoing risks** , which could directly affect our ability to attain our operating goals on schedule and on budget. We are subject to U. S. and certain foreign export and import controls, sanctions, embargoes, anti- corruption laws and anti- money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business. We are subject to export **and import** control ~~and import~~ laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, and various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Controls, and anti- corruption and anti- money laundering laws and regulations, including the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, and other state and national anti- bribery and anti- money laundering laws in the countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, clinical research organizations, contractors and other collaborators and partners from authorizing, promising, offering, providing, soliciting or receiving, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase, and / or to obtain necessary permits, licenses, patent registrations and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government- affiliated hospitals, universities and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, clinical research organizations, contractors and other collaborators and partners, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences. Furthermore, U. S. export control laws and economic sanctions prohibit the provision of certain products and services to countries, governments, and persons targeted by U. S. sanctions. U. S. sanctions that have been or may be imposed as a result of military conflicts in other countries may impact our ability to continue activities at clinical trial sites within regions covered by such sanctions. For example, as a result of the military conflict between Russia and Ukraine, the United States and its European allies announced the imposition of sanctions on certain industry sectors and parties in Russia and the regions of Donetsk and Luhansk in Ukraine, as well as enhanced export controls on certain products and industries. These and any additional sanctions and export controls, as well as any economic countermeasures by the governments of Russia or other jurisdictions, could adversely impact our ability to continue activities at clinical trial sites within regions covered by such sanctions or directly or indirectly disrupt our supply chain. If we fail to comply with export and import regulations and such economic sanctions, penalties could be imposed, including fines and / or denial of certain export privileges. ~~We incur significant costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives. As a public company, we incur significant legal, accounting and other expenses. We are subject to the~~

~~reporting requirements of the Exchange Act, which require, among other things, that we file with the U. S. Securities and Exchange Commission, or SEC, annual, quarterly and current reports with respect to our business and financial condition. In addition, Sarbanes- Oxley, as well as rules subsequently adopted by the SEC, and Nasdaq to implement provisions of Sarbanes- Oxley, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, pursuant to the Dodd- Frank Wall Street Reform and Consumer Protection Act of 2010, the SEC has adopted additional rules and regulations in these areas, such as mandatory " say on pay " voting requirements that apply to us. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. The rules and regulations applicable to public companies have increased and may continue to increase our legal and financial compliance costs and to make some activities more time- consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business. For example, in recent periods obtaining director and officer liability insurance has become more expensive, and we may be required to continue to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.~~ If securities or industry analysts do not publish research or reports or publish unfavorable research or reports 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, our business, our market or our competitors. We currently have limited research coverage by securities and industry analysts. If securities or industry analysts do not continue coverage of our company, the trading price for our stock would be negatively impacted. In the event one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline. ~~If we fail to maintain proper and effective internal control over financial reporting, our ability to produce accurate and timely financial statements could be impaired, investors may lose confidence in our financial reporting and the trading price of our common stock may decline. Pursuant to Section 404 of Sarbanes- Oxley, our management is required to report upon the effectiveness of our internal control over financial reporting. Additionally, our independent registered public accounting firm is required to attest to the effectiveness of our internal control over financial reporting. The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation. To comply with the requirements of being a reporting company under the Exchange Act, we have been required to upgrade our information technology systems; implement additional financial and management controls, reporting systems and procedures; and hire additional accounting and finance staff. If we or our auditors are unable to conclude that our internal control over financial reporting is effective, investors may lose confidence in our financial reporting and the trading price of our common stock may decline. Although we have determined that our internal control over financial reporting was effective as of December 31, 2022, we cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.~~ The increasing focus on environmental sustainability and social initiatives could increase our costs, harm our reputation and adversely impact our financial results. There has been increasing public focus by investors, **employees,** environmental activists, the media ~~and ,~~ governmental and nongovernmental organizations **and other stakeholders** on a variety of environmental, social **, and governance, or ESG,** and other sustainability matters. We may experience pressure to make commitments relating to sustainability matters that affect us, including the design and implementation of specific risk mitigation strategic initiatives relating to sustainability. If we are not effective in addressing environmental, social and other sustainability matters affecting our business, or setting and meeting relevant sustainability goals, our reputation and financial results may suffer. In addition, we may experience increased costs in order to execute upon our sustainability goals and measure achievement of those goals, which could have an adverse impact on our business and financial condition. **Some investors may use third- party ESG ratings and reports to guide their investment strategies and, in some cases, may choose not to invest in us if they believe our ESG practices are inadequate. The criteria by which companies' ESG practices are assessed are evolving, which could result in greater expectations of us and cause us to undertake costly initiatives to satisfy such new criteria. Alternatively, if we elect not to or are unable to satisfy new criteria or do not meet the criteria of a specific third- party provider, some investors may conclude that our policies with respect to ESG are inadequate and choose not to invest in us.** In addition, this emphasis on environmental, social and other sustainability matters has resulted and may result in the adoption of new laws and regulations, including new reporting requirements **. For example, the SEC has announced proposed rules that, among other matters, will establish a framework for reporting of climate- related risks. To the extent the proposed rules impose additional reporting obligations, we could face increased costs** . If we fail to comply with new laws, regulations or reporting

requirements, our reputation and business could be adversely impacted. Changes in tax laws may impact our financial condition and results of operations. New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, or interpreted, changed, modified or applied adversely to us, any of which could adversely affect our business operations and financial performance. We are currently unable to predict whether such changes will occur and, if so, the ultimate impact on our business. To the extent that such changes have a negative impact on us, our suppliers or our customers, including as a result of related uncertainty, these changes may materially and adversely impact our business, financial condition, results of operations and cash flows. We could be subject to securities class action litigation. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management' s attention and resources, which could harm our business.