UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

Form 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2022

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to

Commission File Number: 001-38583

Crinetics Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**26-3744114**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
10222 Barnes Canyon Road, Bldg. #2, San Diego, California	**92121**
(Address of principal executive offices)	**(Zip code)**

Registrant's telephone number, including area code: **(858) 450-6464**

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Trading Symbol(s)**	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001 per share	**CRNX**	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Securities Exchange Act of 1934.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☒
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

As of June 30, 2022 (the last business day of the registrant's most recently completed second fiscal quarter), the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $1 billion, based on the closing price of the registrant's common stock on the Nasdaq Global Select Market on such date of $19.64 per share.

The number of outstanding shares of the registrant's common stock, par value $0.001 per share, as of February 24, 2023 was 53,908,865.

DOCUMENTS INCORPORATED BY REFERENCE

Certain sections of the registrant's definitive proxy statement for the 2023 annual meeting of stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after end of the fiscal year covered by this Form 10-K are incorporated by reference into Part III of this Form 10-K.

CRINETICS PHARMACEUTICALS, INC.
FORM 10-K — ANNUAL REPORT

For the Fiscal Year Ended December 31, 2022

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PART I

Forward-Looking Statements and Market Data

This annual report on Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this annual report, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing and likelihood of success, plans and objectives of management for future operations and future results of anticipated products, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. This annual report on Form 10-K also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "anticipate," "could," "intend," "target," "project," "contemplates," "believes," "estimates," "predicts," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this annual report are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this annual report and are subject to a number of risks, uncertainties and assumptions, including those described in Part I, Item 1A, "Risk Factors." The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

We use our pending trademark Crinetics in this annual report. This annual report also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this annual report appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we or the respective owners will not assert, to the fullest extent under applicable law, any and all rights to these trademarks and tradenames.

Summary of Risk Factors

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 us to delay, limit, reduce 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 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 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 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 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 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.
- 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 face competition from entities that have developed or may develop somatostatin agonist products or other product candidates. If these companies develop 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.
- The trading price of the shares of our common stock could be highly volatile, and purchasers of our common stock could incur substantial losses.

Item 1. Business

Business 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 neuroendocrine tumors complicated by carcinoid syndrome, CRN04777, which is in clinical development for congenital hyperinsulinism, or HI, and CRN04894, which is in clinical development for diseases of excess adrenocorticotrophic hormone, 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 endocrine company which 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 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. 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. NETs 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. 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, branded somatostatin peptide drugs accounted for approximately $2.8 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 patients. The U.S. Food and Drug Administration, or FDA, has granted orphan drug designation for paltusotine for the treatment of acromegaly.

To date, we have conducted multiple Phase 1 and Phase 2 clinical trials and results have shown that paltusotine was generally well tolerated. 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 maintained IGF-1 for up to 103 weeks at levels comparable to prior injected SRL therapy.

We are currently conducting a Phase 3 development program for paltusotine in acromegaly which consists of two placebo-controlled clinical trials. The first of these, the PATHFNDR-1 trial, 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 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. The primary endpoint of both PATHFNDR studies will be the proportion of patients with IGF-1 $\leq 1.0 \times$ ULN at the end of the treatment period on paltusotine as compared to placebo. Enrollment in PATHFNDR-1 was completed in 2022, and 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 the first quarter of 2024. We believe that, if successful, the two trials could support 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, in 2024.

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 data from this study in the second half of 2023.

In February 2022, we entered into a license agreement with Sanwa Kagaku Kenkyusho Co., Ltd., or Sanwa, pursuant to which Sanwa has the exclusive right to develop and commercialize paltusotine in Japan, or the Sanwa License.

CRN04894 (ACTH Antagonist)

CRN04894 is our investigational, oral, nonpeptide product candidate designed to antagonize the ACTH receptor, intended for the treatment of diseases caused by excess ACTH, including 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 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 the United States, there are an estimated 27,000 patients with CAH and over 11,000 patients with Cushing's disease. 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 announced positive topline data from the Phase 1 study. 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 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 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 for this study have begun and data is expected from the study in 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 2023.

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 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 await new therapeutic options, and we are continuously evaluating 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 including polycystic kidney disease, metabolic diseases (including diabetes and obesity) and Graves' Disease (including Thyroid Eye Disease), among other 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 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.

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 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 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 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).

Peptide hormone GPCRs

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 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.

Our product candidates

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. The following table summarizes our product candidate pipeline.

Compound/Program	Indication	Preclin	Phase 1	Phase 2	Phase 3
Paltusotine (SST2 agonist)	Acromegaly				
Paltusotine (SST2 agonist)	Carcinoid Syndrome				
CRN04894 (ACTH antagonist)	Cushing's Disease				
CRN04894 (ACTH antagonist)	Congenital Adrenal Hyperplasia (CAH)				
CRN04777 (SST5 agonist)	Congenital Hyperinsulinism (CHI)				

Somatostatin receptor type 2 agonists for the treatment of acromegaly and neuroendocrine tumors

Our lead product, paltusotine, is an oral selective nonpeptide SST2 agonist in clinical development for the treatment of acromegaly. The FDA 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. We are currently conducting our Phase 3 program of paltusotine in acromegaly patients and topline data is expected in the second half of 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 study in the second half of 2023. In February 2022, we entered into the Sanwa License pursuant to which Sanwa has the exclusive right to develop and commercialize paltusotine in Japan.

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 result in alteration of facial features. 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.

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 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 somatostatin analog (SSA) therapy in adults inadequately controlled by SSA 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 ^{177}Lu 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 neuroendocrine tumors.

Paltusotine overview and clinical development

Paltusotine, our lead product candidate, pioneers a new class of oral selective nonpeptide SST2 agonists designed for the treatment of acromegaly 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 (EC_{50}=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.

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, 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, 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 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.

Based on feedback from our interactions with 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 $\leq 1.0 \times$ ULN at the end of a nine-month treatment period on paltusotine as compared to placebo. We are also conducting a second study, PATHFNDR-2, which is designed as a double-blind, placebo-controlled, twenty-four-week trial in acromegaly patients with elevated IGF-1 levels, who are untreated. Three groups of subjects will be enrolled including subjects with no prior medical therapy (Group 1), subjects who last received medical therapy at least 4 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 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 there will be an equal number of subjects in each stratum. If enrollment in Stratum 2 is 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 $\leq 1.0 \times$ 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 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. Enrollment in PATHFNDR-1 was completed in 2022 and 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 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

the treatment of acromegaly in the United States with an anticipated submission of a New Drug Application, or NDA, in 2024.

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 data from this study in the second half of 2023.

ACTH antagonists for the treatment of 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. 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, initiated clinical studies in patients with Cushing's disease and initiated study activities for a Phase 2 study in patients with CAH.

Background on diseases of ACTH excess

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 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 prevalence of approximately 27,000 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

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 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.

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).

Current treatments and limitations

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.

Preclinical development

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 K_{ATP} 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.

Clinical development

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.

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 2023.

Research Discovery

Patients with many other debilitating endocrine diseases await new therapeutic options, and we are continuously evaluating 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 including polycystic kidney disease, metabolic diseases (including diabetes and obesity) and Graves' Disease (including Thyroid Eye Disease), among other 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 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.

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.). 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 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 neuroendocrine tumors. Camurus, Amryt, POINT Biopharma Global Inc., 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., 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 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. 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., 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 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 unmet medical needs and creates 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 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 Hong Kong, Malaysia, Philippines, Thailand, Vietnam, Chile, Colombia, Argentina, Peru, Venezuela, and Egypt. 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, 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 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, not including any available patent term adjustments or extensions.

We own an issued patent and multiple pending patent applications relating to our SST5 product candidate CRN04777. An issued patent claiming the compound CRN04777 as composition-of-matter has been obtained in the United States and is estimated to expire in 2040, 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 in the United States, three registered trademarks in the UK, and three registered trademarks in the European Union. 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 to build the infrastructure to effectively support the commercialization of our product candidates, 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 will have to invest significant amounts of financial and management resources, some of which will 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. In certain instances, we may consider building our own commercial infrastructure.

Government 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.

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 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; (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 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. 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.

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, 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 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, 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, 2023, we had 210 full-time employees, 55 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.

Insurance

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. Our principal executive offices are located at 10222 Barnes Canyon Road, Bldg. #2, San Diego, California 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 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 related notes 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 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 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

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.

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 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 have incurred significant operating losses since our inception. If our product candidates are not successfully developed and approved, we may never generate any revenue. We have incurred cumulative net losses since our inception and, as of December 31, 2022, we had an accumulated deficit of $439.2 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. A decline in the value of our company could also cause you to lose all or part of your investment.

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 us to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations.

The development of biopharmaceutical product candidates is 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 polycystic kidney disease, metabolic diseases (including

diabetes and obesity) and Graves' Disease (including 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. 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 could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

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, and we may need to seek additional funds sooner than planned, 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 strategic collaborations. We do not currently have any active grants nor do we expect grant revenues to be a material source of future revenue. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. 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 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 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 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 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 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 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 all.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through equity offerings, such as our follow-on public offerings and private placements completed in 2021 and 2022, and under the Sales

Agreement, debt financings or other capital sources, including potentially collaborations, licenses and other similar arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through future collaborations, licenses and other similar arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock.

Risks related to the discovery and development and regulatory approval of our product candidates

We are early in our development efforts and have 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 product candidates or experience significant delays in doing so, our business will be materially harmed.

We are in the early stages of our development efforts and have only three 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 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, we may not be able to generate sufficient revenue to continue our business.

We cannot assure you that we will be able to successfully develop any product candidates.

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. 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, and any product candidates that we are currently developing 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 be forced to abandon our 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.

Preclinical and clinical drug development is expensive and can take many years to complete, and its outcome is inherently uncertain. 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 for 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. In particular, while we have conducted preclinical studies and have obtained Phase 2 results for paltusotine in acromegaly subjects, we do not know how paltusotine will perform in future clinical trials, including 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 many 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 pharmaceutical and 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. 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 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. 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 or will have agreements governing these third parties' services, we have limited influence over their actual performance. If these third parties do not make data available to us, or, if applicable, 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 delays related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical studies;
- obtaining regulatory authorizations to commence 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 refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing their approval of the trial;
- changes to clinical trial protocol;
- 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;
- 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, 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 completing our planned and ongoing clinical trials. We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, 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. In addition, changes in regulatory requirements and policies may occur, 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 for reexamination, which may impact the costs, timing or successful completion of a clinical trial.

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 our clinical trials. These 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 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.

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. 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.

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. Any of these occurrences may harm 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 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.

Subject enrollment, a significant factor in the timing of clinical trials, 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 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 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. We may not be able to initiate or continue clinical trials if we are unable to locate a sufficient number of eligible subjects to participate in the clinical trials required by the FDA or comparable foreign regulatory authorities. In addition, the process of finding and diagnosing subjects may prove costly.

The timing of our clinical trials depends, in part, on the speed at which we can recruit patients to participate in our trials, as well as completion of 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. The eligibility criteria of our clinical trials, once established, will further limit the pool of available trial participants. If 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 future clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. In addition, we expect to rely on CROs and clinical trial sites to ensure proper and 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.

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 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. 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.

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;
- 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 our business, results of operations and prospects.

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.

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution 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, we 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, and the FDA has 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. For example, while we are conducting two Phase 3 clinical trials of paltusotine in distinct patient populations (patients who are on stable doses of SRL 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 FDA or comparable foreign regulatory authorities, as the case may be, may also 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, or inability to obtain, applicable regulatory approval would delay or prevent commercialization of that product candidate and would 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 a result, we may forgo or delay pursuit of opportunities with other product candidates 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 a similar orphan drug designation in the European Union. We have 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.

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. 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 European Union legislation (as implemented into United Kingdom law), however going forward there is a risk that United Kingdom rules will diverge from European Union laws. Although regulatory authorities in the United Kingdom 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 be 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); and 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. 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.

Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose 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 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, preliminary and topline data should be viewed with caution until the final data are available. From time to time, we may also disclose interim data from our clinical studies. 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 preliminary, topline or interim data and final data could significantly harm our business prospects.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and 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, we have used and relied on, and intend to continue to use and rely on, medical institutions, clinical investigators, CROs and consultants to conduct our clinical trials in accordance with our 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 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. Regulatory authorities enforce these GCPs 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. 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 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.

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 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 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. 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 with confidence.

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.

In addition, we may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- failure of third-party manufacturers to comply with regulatory requirements and maintain quality assurance;
- breach of the manufacturing agreement by the third party;
- failure to manufacture our product according to our specifications;
- failure to manufacture our product according to our schedule or at all;
- 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.

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 adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

We are dependent on an international third-party licensee for the development and commercialization of paltusotine in Japan, and may do so 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, 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, allocation of resources and successful commercialization of paltusotine by Sanwa. We also depend on Sanwa to comply with all applicable laws relative to the development and commercialization of our product in Japan. 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 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. 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 manufacture 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 confidentiality agreements, consulting agreements or other similar agreements with our advisors, employees and consultants 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. 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, 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 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 FDA may also require 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 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 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
- injunctions or the imposition of civil or criminal penalties.

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.

In addition, 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.

The FDA's and other regulatory authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay 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 we may not achieve or sustain profitability.

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 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, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the 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;
- the indications for which our product candidates are approved;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA-approved labeling;
- acceptance of a new drug for the relevant indication by healthcare providers and their patients;
- 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 market introduction of our products as well as competitive drugs;
- the effectiveness of our or any of our potential future collaborators' sales and marketing strategies; and
- unfavorable publicity relating to the product.

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.

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 in pricing regulation 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. As a result, increasingly high barriers are being erected to the entry of new products.

We face competition from entities that have developed or may develop somatostatin agonist products or other product candidates. If these companies develop 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.

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. 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.). 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 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 neuroendocrine tumors. Camurus, Amryt, POINT Biopharma Global Inc., 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., 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. 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 adversely affected.

The number of patients suffering from the rare endocrine diseases 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. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. 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.

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.

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. 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, 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 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 industry

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.

Our quarterly and annual operating results may fluctuate significantly, which makes it difficult for us to predict our future operating results. These fluctuations may occur due to a variety of factors, many of which are outside of our control, including, but not limited to:

- the timing and cost of, and level of investment in, research, development, regulatory approval and commercialization activities relating to our product candidates, which may change from time to time;
- coverage and reimbursement policies with respect to our product candidates, if approved, and potential future drugs that compete with our products;
- the cost of manufacturing our product candidates, which may vary depending on the quantity of production and the terms of our agreements with third-party manufacturers;
- expenditures that we may incur to acquire, develop or commercialize additional product candidates and technologies;
- the level of demand for any approved products, which may vary significantly;
- future accounting pronouncements or changes in our accounting policies; and
- the timing and success or failure of preclinical studies or clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance.

This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings 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 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, 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. 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, 2023, we had 210 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, 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.

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 and delete their personal information, opt out of certain personal information sharing, 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 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. 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; however, this new EU-US Data Privacy Framework has not been implemented beyond an 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 of July 16, 2020 have taken a restrictive approach to international data transfers. 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.

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. 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 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.

If product liability 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 could be asserted under state consumer protection acts.

If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit 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;
- 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;
- 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.

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 criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products.

Our employees and independent contractors, including principal investigators, CROs, consultants 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 and vendors may engage in misconduct or other 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 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. 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 our 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 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 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. 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 not realize any benefits from our relationship with Radionetics.

In conjunction with formation of Radionetics, we initially retained a majority equity stake in Radionetics and 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. However, Radionetics will need additional capital to advance its pipeline and our ownership interest may be diminished in connection with future capital raising. In addition, our ability to receive milestone or royalty payments from Radionetics 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 license agreement or research collaboration with Radionetics.

Risks related to our intellectual property

Our success depends on our ability to protect our intellectual property and our proprietary technologies.

Our commercial success depends in part on our ability to obtain and maintain 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 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. 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 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.

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 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 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, 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.

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 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 which could materially adversely affect 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 of our intellectual property rights, including those for our lead programs, 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 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 product candidate(s). 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.

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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. In addition, the issuance of a patent does not give us the right to practice the patented invention. Third parties may have blocking patents that could prevent us from marketing our 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. 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 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, 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, European 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. 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 trademark registration applications in the USPTO, 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.

The trading price of the shares of our common stock could be highly volatile, and purchasers of our common stock could incur substantial losses.

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;
- 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 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 insiders and stockholders;
- general economic, industry and market conditions or other events or factors, many of which are beyond our control, such as the COVID-19 pandemic, inflation, interest rates and the military conflict between Russia and Ukraine;
- additions or departures of key personnel; and
- intellectual property, product liability or other litigation 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 49.7% of our outstanding common stock as of February 24, 2023. 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 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 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, we had federal, state and foreign NOL carryforwards of approximately $254.5 million, $218.0 million and $1.3 million, respectively. The federal NOL carryforwards generated in taxable years beginning after December 31, 2017 of $248.1 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 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 $8.8 million, $6.1 million, and $12.5 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

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 to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information of customers 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 and other social engineering schemes, employee theft or misuse, human error, fraud, denial or degradation of service attacks, 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. 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 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. While we do 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. 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 epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. We rely on third- party 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 were affected by a man-made or natural disaster or other business interruption. 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, 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, 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. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur.

Our general business strategy may be adversely affected by any such economic downturn, 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, it may make any necessary debt or equity financing more difficult, more costly 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, 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 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, environmental activists, the media and governmental and nongovernmental organizations on a variety of environmental, social 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.

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. 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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters consists of a 29,499 square foot facility in San Diego, California. We use our corporate headquarters primarily for corporate, research, development, clinical, regulatory, manufacturing and quality functions. Our lease for this facility expires in August 2025.

On September 9, 2022, we entered into a lease agreement for laboratory and office space in San Diego, California, or the 2022 Lease. We expect to move our corporate headquarters to this new facility in the second half of 2023, upon our substantial completion of improvements.

We believe that our facilities are adequate to meet our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms, if required.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings. From time to time, we may be involved in legal proceedings or subject to claims incident to the ordinary course of business. Regardless of the outcome, such proceedings or claims can have an adverse impact on us because of defense and settlement costs, diversion of resources and other factors, and there can be no assurances that favorable outcomes will be obtained.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock is listed on the Nasdaq Global Select Market under the ticker symbol "CRNX."

Holders of Common Stock

As of February 24, 2023, there were 10 registered holders of record of our common stock. This number was derived from our shareholder records and does not include beneficial owners of our common stock whose shares are held in the name of various dealers, clearing agencies, banks, brokers and other fiduciaries.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

Securities Authorized for Issuance Under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K for information about our equity compensation plans which is incorporated by reference herein.

Stock Performance Graph

The following stock performance graph compares our total stock return with the total return for (i) the Nasdaq Composite Index and the (ii) the Nasdaq Biotechnology Index for the period from July 18, 2018 (the date our common stock commenced trading on the Nasdaq Global Select Market) through December 31, 2022. The figures represented below assume an investment of $100 in our common stock on July 18, 2018. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common stock.

Recent Sales of Unregistered Securities

None.

Issuer Repurchases of Equity Securities

None.

Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion of our financial condition and results of operations in conjunction with the consolidated financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K. This section of this Annual Report on Form 10-K generally discusses 2022 and 2021 items and year-to-year comparisons between 2022 and 2021. Discussions of 2020 items and year-to-year comparisons between 2021 and 2020 that are not included in this Annual Report on Form 10-K can be found in the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 of the Company's Annual Report on Form 10-K for the year ended December 31, 2021.

Overview

We are a clinical-stage pharmaceutical company focused on the discovery, development and commercialization of novel therapeutics for rare 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 neuroendocrine tumors complicated by carcinoid syndrome, CRN04777, which is in clinical development for congenital hyperinsulinism, or HI, and CRN04894, which is in clinical development for diseases of excess adrenocorticotrophic hormone, or ACTH, including Cushing's disease and congenital adrenal hyperplasia. We are advancing additional product candidates through preclinical discovery and development studies in parallel. Our vision is to build the leading endocrine company which 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.

To date, we have devoted substantially all of our resources to drug discovery, conducting preclinical studies and clinical trials, obtaining and maintaining patents related to our product candidates, licensing activities, and the provision of general and administrative support for these operations. We have recognized revenues from various research and development grants and license and collaboration agreements, but do not have any products approved for sale and have not generated any product sales. We have funded our operations primarily through our grant and license revenues, the private placement of our preferred stock, and sales of our common stock As of December 31, 2022, we had unrestricted cash, cash equivalents and investment securities of $334.4 million.

We have incurred cumulative net losses since our inception and, as of December 31, 2022, we had an accumulated deficit of $439.2 million. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical trials and preclinical studies and our expenditures on other research and development activities. We expect our expenses and operating losses will increase substantially as we conduct our ongoing and planned clinical trials, continue our research and development activities and conduct preclinical studies, hire additional personnel, protect our intellectual property and incur costs associated with being a public company, including audit, legal, regulatory, and tax-related services associated with maintaining compliance with exchange listing and Securities and Exchange Commission, or SEC, requirements, director and officer insurance premiums, and investor relations costs.

We do not expect to generate any revenues from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, until such time as we can generate significant revenue from sales of our product candidates, if ever, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potentially collaborations, licenses and other similar arrangements. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements when needed would have a negative impact on our financial condition and could force us to delay, scale back or discontinue the development of our existing product candidates or our efforts to expand our product pipeline.

Australian operations

In January 2017, we established Crinetics Australia Pty Ltd, or CAPL, a wholly-owned subsidiary which was formed to conduct various preclinical and clinical activities for our product and development candidates. We believe CAPL will be

eligible for certain financial incentives made available by the Australian government for research and development expenses. Specifically, the Australian Taxation Office provides for a refundable tax credit in the form of a cash refund equal to 43.5% of qualified research and development expenditures under the Australian Research and Development Tax Incentive Program, or the Australian Tax Incentive, to Australian companies that operate the majority of their research and development activities associated with such projects in Australia. A wholly-owned Australian subsidiary of a non-Australian parent company is eligible to receive the refundable tax credit, provided that the Australian subsidiary retains the rights to the data and intellectual property generated in Australia, and provided that the total revenues of the parent company and its consolidated subsidiaries during the period for which the refundable tax credit is claimed are less than $20.0 million Australian dollars. 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, the actual refund amounts we receive may differ from our estimates.

COVID-19

As we continue to actively advance our programs, we are in close contact with our principal investigators and clinical sites and continue to assess any impacts of the COVID-19 global pandemic on our drug manufacturing, nonclinical activities, and clinical trials, expected timelines, and costs on an ongoing basis. The direct and indirect impacts of COVID-19 on our business could alter our forecasted timelines. For example, the recent lifting of COVID-19 restrictions and subsequent COVID-19 outbreaks in China have delayed our planned recruitment of patients in our PATHFNDR-2 study. We will continue to evaluate the impact of the COVID-19 pandemic on our business.

Financial operations overview

Revenues

To date, our revenue has been mainly derived from grant awards and licenses. As our data exchange performance obligation under the Sanwa License is fulfilled, we expect to recognize as revenues the deferred revenue amounts included in the accompanying consolidated balance sheets as of December 31, 2022. We will recognize royalty and milestone revenues under our license agreements if and when appropriate under the relevant accounting rules (see Note 8 to our consolidated financial statements). We have not generated any revenues from the commercial sale of approved products, and we do not expect to generate revenues from the commercial sale of our product candidates for at least the foreseeable future, if ever.

License revenues

License revenues in 2021 were derived from the majority equity stake obtained in Radionetics pursuant to a Collaboration and License Agreement, under which Radionetics was granted an exclusive world-wide license to our radiotherapeutics technology platform and associated intellectual property for the development of radiotherapeutics and related radio-imaging agents.

License revenues for 2022 were derived from the Sanwa License, under which Sanwa was granted the exclusive right to develop and commercialize paltusotine in Japan.

Clinical supply revenues

On June 14, 2022, the Company and Sanwa, entered into a clinical supply agreement, or the Sanwa Clinical Supply Agreement, whereby the Company is responsible for manufacturing and supplying certain materials to Sanwa for specified activities under the Sanwa License. During the year ended December 31, 2022, we recognized $0.1 million of revenues pursuant to the Sanwa Clinical Supply Agreement.

Grant revenues

Grant revenues for 2020 were derived from 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. There were no grant revenues in 2022 or 2021. We do not currently have any active SBIR Grants nor do we expect grant revenues to be a material source of future funding.

Research and development

To date, our research and development expenses have related primarily to discovery efforts and preclinical and clinical development of our product candidates. Research and development expenses are recognized as incurred and payments made prior to the receipt of goods or services to be used in research and development are capitalized until the goods or services are received.

Research and development expenses include:

- salaries, payroll taxes, employee benefits, and stock-based compensation charges for those individuals involved in research and development efforts;
- external research and development expenses incurred under agreements with contract research organizations, or CROs, investigative sites and consultants to conduct our clinical trials and preclinical and nonclinical studies;
- costs related to manufacturing our product candidates for clinical trials and preclinical studies, including fees paid to third-party manufacturers;
- costs related to compliance with regulatory requirements;
- laboratory supplies; and
- facilities, depreciation and other allocated expenses for rent, facilities maintenance, insurance, equipment and other supplies.

We recognize the Australian Tax Incentive as a reduction of research and development expense. The amounts are determined based on eligible research and development expenditures. The Australian Tax Incentive is recognized when there is reasonable assurance that the Australian Tax Incentive will be received, the relevant expenditure has been incurred, and the amount of the Australian Tax Incentive can be reliably measured.

Our direct research and development expenses consist principally of external costs, such as fees paid to CROs, investigative sites and consultants in connection with our clinical trials, preclinical and non-clinical studies, and costs related to manufacturing clinical trial materials. The majority of our third-party expenses during the three years ended December 31, 2022 related to the research and development of paltusotine, CRN04777, and CRN04894. We deploy our personnel and facility related resources across all of our research and development activities.

Our clinical development costs may vary significantly based on factors such as:

- per patient trial costs;
- the number of trials required for approval;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of patients that participate in the trials;
- number of doses that patients receive;
- drop-out or discontinuation rates of patients;
- potential additional safety monitoring requested by regulatory agencies;
- the duration of patient participation in the trials and follow-up;
- the cost and timing of manufacturing our product candidates;
- the phase of development of our product candidates; and
- the efficacy and safety profile of our product candidates.

We plan to substantially increase our research and development expenses for the foreseeable future as we continue the development of our product candidates and the discovery of new product candidates. We cannot determine with certainty the timing of initiation, the duration or the completion costs of current or future preclinical studies and clinical trials of our product candidates due to the inherently unpredictable nature of preclinical and clinical development. Clinical and preclinical development timelines, the probability of success and development costs can differ materially from expectations. We anticipate that we will make determinations as to which product candidates to pursue and how much funding to direct to each product candidate on an ongoing basis in response to the results of ongoing and future preclinical studies and clinical trials, regulatory developments and our ongoing assessments as to each product candidate's commercial potential. We will need to raise substantial additional capital in the future. In addition, we cannot forecast which product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements.

General and administrative

General and administrative expenses consist primarily of salaries and employee-related costs, including stock-based compensation, for personnel in executive, finance and other administrative functions. Other significant costs include facility-related costs, legal fees relating to intellectual property and corporate matters, professional fees for accounting and consulting services, insurance costs, and commercial planning expenses. We anticipate that our general and administrative expenses will increase in the future to support our continued research and development activities and, if any of our product candidates receive marketing approval, commercialization activities. We also anticipate increased expenses related to audit, legal,

regulatory, and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums, and investor relations costs associated with operating as a public company.

Critical Accounting Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those listed below. We base our estimates on historical experience, known trends and events, information received from third parties and various other factors that we believe are reasonable under the circumstances at the time the estimates are made, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. There were no material differences between estimates and actual results for the years presented in the accompanying consolidated financial statements.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies and estimates to be most critical to the preparation of our consolidated financial statements.

Accrued expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our vendors in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to research and development activities on our estimates of the services received and efforts expended pursuant to quotes and contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense accordingly. Advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Stock-based compensation expense

Stock-based compensation expense represents the estimated grant date fair value of the Company's equity awards, consisting of stock options, restricted stock units and shares issued under the Company's Employee Stock Purchase Plan, or ESPP, recognized over the requisite service period of such awards (usually the vesting period) on a straight-line basis. We estimate the fair value of all stock option and ESPP grants using the Black-Scholes option pricing model and recognize forfeitures as they occur. Restricted stock units are valued using the grant date stock price.

Estimating the fair value of equity awards as of the grant date using valuation models, such as the Black-Scholes option pricing model, is affected by assumptions regarding a number of complex variables, including the expected stock price volatility, the risk-free interest rate, the expected term of stock options, the expected dividend yield and the fair value of the underlying common stock on the date of grant. Changes in the assumptions can materially affect the fair value and ultimately how much stock-based compensation expense is recognized. These inputs are subjective and generally require significant analysis and judgment to develop.

Due to the lack of an adequate history of a public market for the trading of our common stock and a lack of adequate company-specific historical and implied volatility data that we believe is indicative of the expected future volatility, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For these analyses, we have selected companies with comparable characteristics to ours, including enterprise value, risk profiles, and position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily close prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until sufficient historical information regarding the volatility of our common stock price becomes available or until we believe the volatility of our own market-traded shares best represents expected volatility. We have estimated the expected life of our employee stock options using the "simplified" method, whereby the expected life equals the average of the vesting term and the original contractual term of the option. The expected term for employee stock purchase plan awards represents the term the awards are expected to be outstanding. The risk-free interest rates for periods within the expected life of the awards are based on the yields of zero-coupon U.S. treasury securities.

Investment in Radionetics

We first analyze our investment in another entity to determine if the entity is a variable interest entity, or VIE, and if so, whether we are the primary beneficiary requiring consolidation. An entity is considered a VIE if (1) the entity does not have enough equity to finance its own activities without additional support, (2) the entity's at-risk equity holders lack the characteristics of a controlling financial interest, or (3) the entity is structured with non-substantive voting rights. VIEs are consolidated by the primary beneficiary, which is the entity that has both the power to direct the activities that most significantly impact the VIE's economic performance and the obligation to absorb losses or the right to receive benefits from the VIE that potentially could be significant to the VIE. Variable interests in a VIE can be contractual, ownership, or other financial interests. We re-assess our investment upon reconsideration events to determine whether we are the primary beneficiary of the VIE, in which case we would consolidate the VIE. If it has been determined that we are not the primary beneficiary or do not have control but do have the ability to exercise significant influence over the VIE, we account for the unconsolidated investment under the equity method of accounting.

Radionetics is considered to be a VIE because it cannot finance its activities without subordinated financial support. We maintain an equity interest in Radionetics and account for our investment under the equity method of accounting as we are not the primary beneficiary of Radionetics but have the ability to exercise significant influence. The valuation method and primary inputs used in valuing the Radionetics investment are discussed below under Revenue Recognition. We record our share of Radionetics income (loss) outside of operations in the statements of operations and comprehensive loss on a quarterly lag. Since our investment in Radionetics was obtained on October 15, 2021, we recorded our share of income (loss) beginning in the first quarter of 2022. Our equity method investment in Radionetics was written down to zero during the first quarter of 2022 as a result of the allocation of our share of losses of the investee.

Valuation of Financial Instruments

Investment Securities

We hold investment securities that consist of highly liquid, investment grade debt securities. We determine the fair value of our investment securities based upon one or more valuations reported by its investment accounting and reporting service provider. The investment service provider values the securities using a hierarchical security pricing model that relies primarily on valuations provided by an industry-recognized valuation service. Such valuations may be based on trade prices in active markets for identical assets or liabilities (Level 1 inputs) or valuation models using inputs that are observable either directly or indirectly (Level 2 inputs), such as quoted prices for similar assets or liabilities, yield curves, volatility factors, credit spreads, default rates, loss severity, current market and contractual prices for the underlying instruments or debt, and broker and dealer quotes, as well as other relevant economic measures.

Derivative Asset

Derivatives are recorded at fair value and changes in fair value are recorded through the statements of operations and comprehensive loss each period. We have a single derivative instrument, a warrant from Radionetics, or the Radionetics Warrant, to purchase the greater of 3,407,285 additional shares of common stock or the number of additional shares of common stock that would allow us to maintain an aggregate equity interest of 22% of the fully diluted capitalization of Radionetics. We record the Radionetics Warrant as long-term on the balance sheets due to the lack of marketability, such that it is not expected to be available for current operations. Changes in fair value of the Radionetics Warrant are recognized in other income (expense) in the accompanying consolidated statements of operations and comprehensive loss.

The valuation method and inputs used in valuing the Radionetics Warrant are discussed below under Revenue Recognition. Such valuation is based on valuations provided by a third-party valuation specialist using unobservable inputs due to little to no market data (Level 3 inputs).

Revenue Recognition

We have generated revenue from licensing arrangements, a clinical supply agreement, as well as from grants from government agencies. We have recognized revenues when, or as, the promised goods or services are transferred to customers in an amount that reflects the consideration to which we expect to be entitled in exchange for those services. To determine revenue recognition for arrangements, we perform the following five steps: (1) identify the contract(s) with a customer; (2) identify the performance obligation(s) in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligation(s) in the contract; and (5) recognize revenue when (or as) the performance obligation(s) are satisfied. At contract inception, we assess the goods or services promised within each contract, assess whether each promised good or service is distinct and identify those that are performance obligations. We recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when, or as, the performance obligation is satisfied.

We consider a variety of factors in determining the appropriate estimates and assumptions under the arrangements, such as whether the elements are distinct performance obligations, whether there are observable standalone prices, whether the license is functional or symbolic, and whether the Company is acting as the agent or principal. We evaluate each performance obligation to determine if it can be satisfied and recognized as revenue at a point in time or over time.

License Revenues

We have entered into licensing and collaboration agreements that mainly include the following: (i) upfront considerations (cash and noncash); (ii) payments associated with achieving certain milestones; and (iii) royalties based on specified percentages of net product sales, if any. At the initiation of an agreement, we analyze each unit of account within the contract to determine if the counterparty is a customer in the context of the unit of account.

We evaluate each performance obligation to determine if it can be satisfied and recognized as revenue at a point in time or over time.

At the inception of arrangements that include variable consideration, we use judgment to estimate the amount of variable consideration to include in the transaction price using the most likely method. If it is probable that a significant revenue reversal will not occur, then the estimated amount is included in the transaction price. Milestone payments that are not within our or the licensee's control, such as regulatory approvals, are not included in the transaction price until those approvals are received. At the end of each reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint and, as necessary, adjust the estimate of the overall transaction price. Any adjustments will be recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

We develop estimates of the standalone selling price for each distinct performance obligation. Variable consideration that relates specifically to efforts to satisfy specific performance obligations is allocated entirely to those performance obligations. Other components of the transaction price are allocated based on the relative standalone selling price, over which we have applied significant judgment. We develop assumptions that require judgment to determine the standalone selling price for license-related performance obligations under the adjusted market assessment approach, which may include forecasted revenues, development timelines, discount rates and probabilities of success. We estimate the standalone selling price for the data exchange performance obligation by forecasting the expected costs of satisfying the performance obligation plus a predetermined margin (see Note 8 to our consolidated financial statements).

In the case of a license that is a distinct performance obligation, we recognize revenue allocated to the license from non-refundable, up-front fees at the point in time when the license is transferred to the licensee and the licensee can use and benefit from the license. For licenses that are bundled with other distinct or combined obligations, we use judgment to assess the nature of the performance obligation to determine whether the performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. If the performance obligation is satisfied over time, then we evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

The selection of the method to measure progress towards completion requires judgment and is based on the nature of the products or services to be provided. Revenue is recorded proportionally as costs are incurred. We have used the cost-to-cost measure of progress because it best depicts the transfer of control to the customer which occurs as we incur costs. Under the cost-to-cost measure of progress, the extent of progress towards completion is measured based on the ratio of costs incurred to date to the total estimated costs at completion of the performance obligation, which is considered an input method. We use judgment to estimate the total cost of these performance obligations, which include subcontractors' costs, labor, materials, other direct costs and an allocation of indirect costs. We evaluate these cost estimates and the progress each reporting period and, as necessary, we adjust the measure of progress and related revenue recognition.

Sales-based milestones and royalties are recognized at the later of when the subsequent sale or usage occurs or the performance obligation for which some or all of the sales-based milestones and royalties have been allocated to has been satisfied or partially satisfied.

We engaged a third-party valuation specialist to determine the estimated fair value of these upfront noncash considerations received which consisted of the Radionetics common stock and Radionetics Warrant. The valuation specialist utilized a cost approach to determine the implied value of Radionetics' equity since it was newly formed with early development stage technology from the collaboration and license agreement, or Radionetics License, for which there are not reliable long-term forecasts. Next, the total equity value was allocated to various share classes using the current value method and option pricing method. The current value method allocates the value of the business to the shareholders' given consideration of senior obligations such as debt, equity certificates and other preferred equity. The option pricing method entails allocating the total shareholders' equity value to the various share classes based upon their respective claims on a series of call options with strike prices at various value levels depending upon the rights and preferences of each class.

Estimating the fair value of the Radionetics common stock and Radionetics Warrant is affected by assumptions regarding a number of complex variables, including the expected term for a liquidity event, the risk-free interest rate and stock price volatility. Changes in the assumptions can materially affect the value of license revenues, initial investment in Radionetics, and the Radionetics Warrant. These inputs are subjective and generally require significant analysis and judgment to develop.

We estimated the expected term based on the expected time to a liquidity event. The risk-free interest rate was based on the yields of zero-coupon U.S. treasury securities. Volatility was estimated based upon an analysis of historical equity and asset volatilities of companies deemed comparable to Radionetics. The valuation amounts were adjusted by a discount for lack of marketability to account for the lack of liquidity an owner of the interest would experience for common stock in an early-stage company.

Although we do not expect our estimates to be materially different from actuals, if our estimates of the expected total costs and timing of certain activities differ from the actual cost and timing of those activities, it could result in us reporting license revenues related to the data exchange that are too high or too low in any particular period.

Estimating the standalone selling price of the license performance obligation is affected by assumptions regarding a number of variables discussed above. While not expected, material changes in these initial assumptions can affect the value of license revenues. These inputs are subjective and generally require significant analysis and judgment to develop.

Grant Revenues

Our grant revenues are derived from SBIR Grants. Our performance obligation under SBIR Grants consists of research activities and we recognize SBIR Grants revenue over time as reimbursable grant costs are incurred up to pre-approved award limits within the budget period. The costs associated with these reimbursements are reflected as a component of research and development expense.

Results of Operations

Comparison of the years ended December 31, 2022 and 2021.

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021 (*in thousands*):

	Year ended December 31,		Dollar
	2022	2021	Change
Revenues	$ 4,737	$ 1,078	$ 3,659
Operating expenses:			
Research and development	130,225	84,255	45,970
General and administrative	42,394	24,525	17,869
Total operating expenses	172,619	108,780	63,839
Loss from operations	(167,882)	(107,702)	(60,180)
Other income (expense), net	4,974	61	4,913
Loss before equity method investment	(162,908)	(107,641)	(55,267)
Loss on equity method investment	(1,010)	—	(1,010)
Net loss	$ (163,918)	$ (107,641)	$ (56,277)

Revenues. During the year ended December 31, 2022, we recognized $4.7 million of license revenues related to the Sanwa License. During the year ended December 31, 2021, we recognized $1.1 million of license revenues related to upfront noncash considerations under the Radionetics License.

Research and development expenses. Research and development expenses were $130.2 million and $84.3 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $25.3 million associated with our clinical and nonclinical activities for paltusotine, CRN04894, CRN04777 and our other clinical and preclinical programs, an increase in personnel costs of $16.2 million due to increase in headcount, an increase in consulting and outside services of $3.8 million and an increase in other corporate and travel expenditures of $1.0 million.

The following table summarizes our primary external and internal research and development expenses for the years ended December 31, 2022 and 2021 (*in thousands*):

	Year ended December 31,		Dollar
	2022	2021	Change
External research and development expenses:			
Clinical trials	$ 38,801	$ 25,273	$ 13,528
Contract manufacturing	18,962	13,448	5,514
Preclinical studies	12,758	6,583	6,175
Other external research and development	8,206	4,788	3,418
Total external research and development expenses	78,727	50,092	28,635
Internal expenses:			
Personnel	46,741	30,581	16,160
Other internal research and development	4,757	3,582	1,175
Total internal research and development expenses	51,498	34,163	17,335
Total research and development expenses	$ 130,225	$ 84,255	$ 45,970

The following table summarizes our primary external and internal research and development expenses for the years ended December 31, 2021 and 2020 (*in thousands*):

	Year ended December 31,		Dollar
	2021	2020	Change
External research and development expenses:			
Clinical trials	$ 25,273	$ 14,688	$ 10,585
Contract manufacturing	13,448	12,850	598
Preclinical studies	6,583	4,499	2,084
Other external research and development	4,788	3,665	1,123
Total external research and development expenses	50,092	35,702	14,390
Internal expenses:			
Personnel	30,581	18,326	12,255
Other internal research and development	3,582	2,970	612
Total internal research and development expenses	34,163	21,296	12,867
Total research and development expenses	$ 84,255	$ 56,998	$ 27,257

The following table summarizes our research and development expenses by program for the years ended December 31, 2022 and 2021 (*in thousands*):

	Year ended December 31,		Dollar
	2022	2021	Change
Paltusotine	$ 55,680	$ 34,337	$ 21,343
CRN04894	11,735	8,152	3,583
CRN04777	13,664	11,664	2,000
Other	49,146	30,102	19,044
Total research and development expenses	$ 130,225	$ 84,255	$ 45,970

Research and development expenses for our paltusotine clinical studies were $55.7 million and $34.3 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to increased supplies and spending on

manufacturing and development activities of $19.5 million and an increase in personnel costs of $2.6 million due to increase in headcount.

Research and development expenses for our CRN04894 clinical studies were $11.7 million and $8.2 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $2.7 million and an increase in personnel costs of $1.1 million due to increase in headcount.

Research and development expenses for our CRN04777 clinical studies were $13.7 million and $11.7 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $0.7 million and an increase in personnel costs of $0.8 million due to increase in headcount.

Research and development expenses for our other programs and were $49.1 million and $30.1 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $2.5 million, an increase in personnel costs of $11.7 million due to increase in headcount, an increase in consulting and outside services of $3.9 million and increase in other corporate and travel expenditures of $0.9 million.

The following table summarizes our research and development expenses by program for the years ended December 31, 2021 and 2020 (*in thousands*):

	Year ended December 31,		Dollar
	2021	2020	Change
Paltusotine	$ 34,337	$ 27,780	$ 6,557
CRN04894	8,152	5,576	2,576
CRN04777	11,664	6,253	5,411
Other	30,102	17,389	12,713
Total research and development expenses	$ 84,255	$ 56,998	$ 27,257

Research and development expenses for our paltusotine clinical studies were $34.3 million and $27.8 million for the years ended December 31, 2021 and 2020, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $3.9 million and an increase in personnel costs of $2.0 million due to increase in headcount.

Research and development expenses for our CRN04894 clinical studies were $8.2 million and $5.6 million for the years ended December 31, 2021 and 2020, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $2.8 million.

Research and development expenses for our CRN04777 clinical studies were $11.7 million and $6.3 million for the years ended December 31, 2021 and 2020, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $5.8 million.

Research and development expenses for our other programs and were $30.1 million and $17.4 million for the years ended December 31, 2021 and 2020, respectively. The change was primarily due to increased supplies and spending on manufacturing and development activities of $0.8 million, an increase in personnel costs of $10.6 million due to increase in headcount and an increase in consulting and outside services of $1.0 million.

General and administrative expenses. General and administrative expenses were $42.4 million and $24.5 million for the years ended December 31, 2022 and 2021, respectively. The change was primarily due to an increase in personnel costs of $10.8 million due to increase in headcount, an increase in professional services and outside services of $5.5 million, and an increase in other corporate expenditures of $1.1 million.

Other income (expense). Other income (expense), net was $5.0 million and $0.1 million for the years ended December 31, 2022 and 2021, respectively. The increase was primarily due to income generated by our investment securities and increase in the value of our warrant.

Cash Flows

We have incurred cumulative net losses and negative cash flows from operations since our inception and anticipate we will continue to incur net losses for the foreseeable future. As of December 31, 2022, we had an accumulated deficit of $439.2 million and unrestricted cash, cash equivalents and investment securities of $334.4 million.

The following table provides information regarding our cash flows for each of the years in the two-year period ended December 31, 2022 (*in thousands*):

	Years ended December 31,	
	2022	2021
Net cash used in operating activities	$ (115,205)	$ (88,588)
Net cash used in investing activities	(173,980)	(56,483)
Net cash provided by financing activities	121,963	252,679
Net change in cash, cash equivalents and restricted cash	$ (167,222)	$ 107,608

Comparison of the years ended December 31, 2022 and 2021

Operating Activities. Net cash used in operating activities was $115.2 million and $88.6 million for the years ended December 31, 2022 and 2021, respectively. The increase in cash used in operations was primarily attributable to the development and manufacturing supplies and activities associated with paltusotine, CRN04777, CRN04894, and our other clinical and preclinical programs, and higher personnel costs partially offset by the $13.0 million upfront payment received upon the execution of the Sanwa License in February 2022, of which $4.7 million was recognized as license revenues during the year ended December 31, 2022. The net cash used in operating activities during the year ended December 31, 2022 was primarily due to our net loss of $163.9 million adjusted for $30.1 million of noncash charges, primarily for stock-based compensation and loss on the investment in Radionetics, and a $18.6 million change in operating assets and liabilities. The net cash used in operating activities during the year ended December 31, 2021 was primarily due to our net loss of $107.6 million, adjusted for $18.0 million of noncash charges, including stock-based compensation, depreciation expense, noncash license revenues, and a $1.1 million change in our operating assets and liabilities.

Investing activities. Investing activities consist primarily of purchases and maturities of investment securities and, to a lesser extent, the cash outflow associated with purchases of property and equipment. Such activities resulted in net cash outflows of approximately $174.0 million during the year ended December 31, 2022, compared to the net cash outflows of approximately $56.5 million during the year ended December 31, 2021.

Financing activities. Net cash provided by financing activities was $122.0 million and $252.7 million for the years ended December 31, 2022 and 2021, respectively. The net cash provided by financing activities during 2022 and 2021 resulted from proceeds received from the sale of common stock in our underwritten follow-on offerings and cash received from the exercise of stock options.

Liquidity and Capital Resources

At December 31, 2022, we had unrestricted cash, cash equivalents and investment securities of $334.4 million. Based on our current and anticipated level of operations, we believe that our cash, cash equivalents and short-term investments will be sufficient to meet our anticipated obligations for at least one year from the date this Annual Report on Form 10-K is filed with the SEC. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Additionally, the process of testing product candidates in clinical trials is costly, and the timing of progress and expenses in these trials is uncertain.

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 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 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 personnel and consultants as our preclinical and clinical activities increase;
- the timing and the extent of any Australian Tax Incentive refund and future grant revenues 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 terms and timing of establishing and maintaining collaborations, licenses and other 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 future equity offerings by Radionetics.

Until such time, if ever, as we can generate substantial product revenues to support our cost structure, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potentially collaborations, licenses and other similar arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be or could be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise funds through collaborations, licenses and other similar arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or may reduce the value of our common stock. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

In August 2019, we entered into a Sales Agreement, or the Sales Agreement, with SVB Leerink LLC and Cantor Fitzgerald & Co., or collectively, the Sales Agents, under which we may, from time to time, sell shares of our common stock through the Sales Agents, or the ATM Offering. Sales of our common stock made pursuant to the Sales Agreement will be made directly on or through the Nasdaq Global Select Market under our effective shelf Registration Statement on Form S-3 filed on August 10, 2021, or the 2021 Shelf Registration Statement, and a prospectus supplement filed on August 12, 2022 relating to the offer and sale of up to $150.0 million of shares of our common stock in the ATM Offering by means of ordinary brokers' transactions at market prices. Additionally, under the terms of the Sales Agreement, we may also sell shares of our common stock through the Sales Agents, on the Nasdaq Global Select Market or otherwise, at negotiated prices or at prices related to the prevailing market price. We are not obligated to, and we cannot provide any assurances that we will continue to, make any sales of the shares under the Sales Agreement. The Sales Agreement may be terminated by either Sales Agent (with respect to itself) or us at any time upon 10 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. We will pay the Sales Agents a commission for their services in acting as agent in the sale of common stock in an amount equal to 3% of the gross sales price per share sold. During 2020, we issued 275,764 shares of common stock in the ATM Offering for net proceeds of $6.4 million, after deducting commissions, pursuant to our Shelf Registration Statement on Form S-3, which became effective on August 29, 2019, or the 2019 Shelf Registration Statement. The 2019 Shelf Registration Statement included a prospectus covering the offering, issuance and sale of up to $75.0 million of our common stock from time to time through the ATM Offering. The 2019 Shelf Registration Statement expired on August 29, 2022. No shares were issued under the ATM Offering during the years ended December 31, 2022 and 2021.

On April 17, 2020, we completed a public offering of 8,222,500 shares of our common stock at a public offering price of $14.00 per share. We received proceeds of approximately $107.9 million from that offering, net of offering discounts and commissions and offering costs of $7.3 million.

On April 12, 2021, we completed an underwritten follow-on offering of 4,562,044 shares of our common stock at a price to the public of $16.44 per share. Proceeds from the offering were approximately $72.6 million, net of underwriting discounts and commissions and offering costs of $2.4 million.

On July 28, 2021, we entered into a stock purchase agreement for the private placement of 851,306 shares of our common stock at a price of $17.62 per share, or the Private Placement, which shares were issued on July 30, 2021. The Private Placement yielded net proceeds of $15.0 million.

On August 10, 2021, we filed the 2021 Shelf Registration Statement with the SEC for the future sale of an unlimited amount of common stock, preferred stock, debt securities, depositary shares, warrants and rights, and the resale of up to 851,306 shares by the investor who purchased shares in the Private Placement. The securities may be offered from time to time, separately or together, directly by us, by selling security holders, or through underwriters, dealers or agents at amounts, prices, interest rates and other terms to be determined at the time of the offering.

On October 21, 2021, we completed an underwritten follow-on offering of 8,712,400 shares of our common stock at a price to the public of $19.80 per share. Proceeds from the offering were approximately $162.0 million, net of underwriting discounts and commissions and offering costs of $10.5 million.

On April 18, 2022, we completed an underwritten follow-on offering of 5,625,563 shares of our common stock at a price to the public of $22.22 per share. Net proceeds from the offering were approximately $117.2 million, after underwriting discounts and commissions and offering costs of approximately $7.8 million.

As discussed above, on August 12, 2022, we filed with the SEC a prospectus supplement to the 2021 Shelf Registration Statement pursuant to Rule 424(b) under the Securities Act of 1933, as amended, relating to the offer and sale of up to $150 million of shares of our common stock from time to time to or through the Sales Agents pursuant to the Sales Agreement.

2022 Lease

On September 9, 2022, we entered into a lease agreement for laboratory and office space in San Diego, California, or the 2022 Lease. We expect to move our corporate headquarters to this new facility upon our substantial completion of improvements and written landlord consent, which is expected to occur in the second half of 2023.

Under the terms of the 2022 Lease, our expected future monthly minimum lease payments of $0.5 million, with six months of rent abatement in the first year, start on the earlier of (i) the date which is ten (10) months after substantial completion of demolition work, or (ii) the date of the substantial completion of improvements and first occupancy for business purposes, and the term expires on the date immediately preceding the one hundred thirty-seventh (137th) monthly anniversary of this lease payment start date. Lease payments are subject to annual 3% increases. We are also responsible for certain operating expenses and taxes during the term of the 2022 Lease. The 2022 Lease provides us with specified tenant improvement and landlord work allowances. We have (i) two options to extend the term of the 2022 Lease for an additional period of five (5) years each, and (ii) a right of first offer on adjacent space to the new facility, subject to the terms and conditions of the 2022 Lease.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Interest Rate Risk

Our cash, cash equivalents and investment securities consist of cash held in readily available checking and money market accounts as well as short-term debt securities. We are exposed to market risk related to fluctuations in interest rates and market prices. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of United States interest rates. However, because of the short-term nature of the instruments in our portfolio, a sudden change in market interest rates would not be expected to have a material impact on our financial condition or results of operations.

Foreign Currency

We contract with vendors, CROs and investigational sites in several foreign countries, including countries in South America, Europe and the Asia Pacific. As such, we have exposure to fluctuations in foreign currency rates in connection with these agreements. We do not hedge our foreign currency exchange rate risk. We believe this exposure to be immaterial and, to date, we have not incurred any material adverse effects from foreign currency changes on these contracts.

In January 2017, we formed CAPL, a wholly-owned subsidiary in Australia, which exposes us to foreign currency exchange rate risk. The functional currency of CAPL is the United States dollar. Assets and liabilities of our foreign subsidiary that are not denominated in the functional currency are remeasured into U.S. dollars at foreign currency exchange rates in effect at the balance sheet date except for nonmonetary assets and capital accounts, which are remeasured at historical foreign currency exchange rates in effect at the date of transaction. Expenses are generally remeasured at foreign currency exchange rates which approximate average rates in effect during each period. Net realized and unrealized gains and losses from foreign currency transactions and remeasurement are reported in other income (expense), net, in the consolidated statements of operations and comprehensive loss and totaled approximately ($28,000) and $107,000 for the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the impact of a theoretical 10% change in the exchange rate of the Australian dollar would not result in a material gain or loss. To date, we have not hedged exposures denominated in foreign currencies.

Inflation Risk

Inflation has increased during the period covered by this Annual Report on Form 10-K, and is expected to continue to increase for the near future. Inflationary factors, such as increases in the cost of our materials, supplies, and overhead costs may adversely affect our operating results. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may experience some adverse effect if inflation rates continue to rise. Significant adverse changes in inflation and prices in the future could result in material losses.

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements and the report of our independent registered accounting firm required pursuant to this item are incorporated by reference herein from the applicable information included in Item 15 of this report and are presented beginning on page F-1.

Item 9. Changes and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and our principal financial officer, as appropriate, to allow for timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and management is necessarily required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, control may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

As of December 31, 2022, we carried out an evaluation, under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on this evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2022.

Changes in Internal Control over Financial Reporting

There has been no change in our internal control over financial reporting during the quarter ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Management's Annual Report on Internal Control over Financial Reporting.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP. Our internal control over financial reporting includes those policies and procedures that: (i) pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets, (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors, and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements. Because of its inherent limitations, internal controls over financial reporting may not prevent or detect all misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

As of December 31, 2022, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013). Based on this assessment, our management concluded that, as of December 31, 2022, our internal control over financial reporting was effective based on those criteria.

BDO USA, LLP, the independent registered public accounting firm that audited the consolidated financial statements included in this Annual Report on Form 10-K, was engaged to attest to and report on the effectiveness of the Company's internal control over financial reporting as of December 31, 2022, as stated in its report below.

Report of Independent Registered Public Accounting Firm

Shareholders and Board of Directors
Crinetics Pharmaceuticals, Inc.
San Diego, California

Opinion on Internal Control over Financial Reporting

We have audited Crinetics Pharmaceuticals, Inc.'s (the "Company's") internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (the "COSO criteria"). In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) ("PCAOB"), the consolidated balance sheets of the Company as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2022, and the related notes and our report dated February 28, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying "Item 9A, Management's Report on Internal Control over Financial Reporting". Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit of internal control over financial reporting in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ BDO USA, LLP

San Diego, California

February 28, 2023

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission in connection with our 2023 Annual Meeting of Stockholders, or the Definitive Proxy Statement, which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2022, under the headings "Election of Directors," "Corporate Governance," "Our Executive Officers," and, if applicable, "Delinquent Section 16(a) Reports," and is incorporated herein by reference.

Code of Business Conduct and Ethics

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors and employees, which is available on our website at www.crinetics.com. The Code of Business Conduct and Ethics contains general guidelines for conducting the business of our company consistent with the highest standards of business ethics and is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (i) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (ii) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

Item 11. Executive Compensation.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Executive Compensation and Other Information," and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Security Ownership of Certain Beneficial Owners and Management," and is incorporated herein by reference.

Information required by Item 201(d) of Regulation S-K will be contained in our Definitive Proxy Statement under the heading "Executive Compensation and Other Information" and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

Information required by this item will be contained in our Definitive Proxy Statement under the headings "Certain Relationships and Related Person Transactions," "Board Independence" and "Committees of the Board of Directors" and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Independent Registered Public Accountants' Fees," and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) Documents filed as a part of this report:

(1) Financial Statements.

The financial statements of Crinetics Pharmaceuticals, Inc., together with the reports thereon of BDO USA, LLP, an independent registered public accounting firm, are included in this Annual Report on Form 10-K.

(2) Financial Statement Schedules.

All schedules are omitted because they are not applicable, or the required information is shown in the financial statements or notes thereto.

(3) Exhibits.

A list of exhibits to this Annual Report on Form 10-K is set forth on the Exhibit Index immediately preceding the signature page and is incorporated herein by reference.

Item 16. Form 10-K Summary

None.

CRINETICS PHARMACEUTICALS, INC.
INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

Stockholders and Board of Directors
Crinetics Pharmaceuticals, Inc.
San Diego, California

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Crinetics Pharmaceuticals, Inc. (the "Company") as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with accounting principles generally accepted in the United States of America.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) ("PCAOB"), the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control – Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO") and our report dated February 28, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing separate opinions on the critical audit matter or on the accounts or disclosures to which it relates.

Clinical Trial Accruals

As described in Note 2 to the consolidated financial statements, the Company recognizes costs incurred for clinical trial related activities as research and development expenses based on its evaluation of its vendors' progress toward completion of specific tasks. When payment terms under the related contracts do not align with the pattern of costs incurred, the Company is required to estimate the outstanding obligations as of period end. In estimating the vendors' progress toward completion of specific tasks, the Company uses data such as patient enrollment, clinical site activations and vendor costs incurred. As of December 31, 2022, the Company recorded $1.9 million in clinical trial accruals.

We identified clinical trial accruals as a critical audit matter due to significant management judgment to estimate the progress toward completion of specific tasks that includes patient enrollment, clinical site activations, and vendor costs incurred that is dependent upon data and information from internal clinical personnel and third-party service providers. Auditing these elements involved especially challenging auditor judgment due to the nature and extent of audit effort to address these matters.

The primary procedures we performed to address this critical audit matter included:

- Testing the appropriate measurement of clinical trial accruals by obtaining and inspecting significant agreements and amendments, evaluating the Company's documentation of trial progress and status (including consideration of measures such as patient enrollment, clinical site activations, and vendor costs incurred), and confirming clinical trial billings, payments and expenses with vendors and testing a sample of transactions.
- Testing the completeness of the Company's clinical trial accruals by (i) evaluating internal materials and publicly available information (such as press releases and public databases that track clinical trials), (ii) inquiring of clinical staff to gain an understanding of the status of significant on-going clinical trials, and (iii) testing a sample of invoices received after year-end.

/s/ BDO USA, LLP

We have served as the Company's auditor since 2016.

San Diego, California

February 28, 2023

CRINETICS PHARMACEUTICALS, INC.

Consolidated Balance Sheets
(In thousands, except per share amounts)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 32,672	$ 200,695
Investment securities	301,753	133,012
Prepaid expenses and other current assets	10,759	11,013
Total current assets	345,184	344,720
Property and equipment, net	3,500	2,825
Operating lease right-of-use asset	1,486	1,892
Derivative asset	668	68
Investment in Radionetics	—	1,010
Restricted cash	1,301	500
Other assets	37	—
Total assets	$ 352,176	$ 351,015
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 15,351	$ 8,468
Accrued compensation and related expenses	9,081	6,588
Deferred revenue	2,240	—
Other current liabilities	1,051	939
Total current liabilities	27,723	15,995
Operating lease liability, non-current	2,024	3,074
Deferred revenue, non-current	6,101	—
Unvested stock liability	—	2
Total liabilities	35,848	19,071
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Preferred stock, $0.001 par; 10,000 shares authorized, no shares issued or outstanding at December 31, 2022 or 2021	—	—
Common stock and paid-in capital, $0.001 par; 200,000 shares authorized, 53,877 shares issued and outstanding at December 31, 2022; 47,598 and 47,597 shares issued and outstanding at December 31, 2021	759,432	607,581
Accumulated other comprehensive loss	(3,931)	(382)
Accumulated deficit	(439,173)	(275,255)
Total stockholders' equity	316,328	331,944
Total liabilities and stockholders' equity	$ 352,176	$ 351,015

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS, INC.

Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except per share data)

	Year ended December 31,		
	2022	2021	2020
Revenues:			
Revenues	$ 4,737	$ 1,078	$ —
Grant revenues	—	—	71
Total revenues	4,737	1,078	71
Operating expenses:			
Research and development	130,225	84,255	56,998
General and administrative	42,394	24,525	18,026
Total operating expenses	172,619	108,780	75,024
Loss from operations	(167,882)	(107,702)	(74,953)
Other income (expense):			
Interest income	4,317	157	991
Change in fair value of derivative asset	600	—	—
Other income (expense), net	57	(96)	150
Total other income, net	4,974	61	1,141
Loss before equity method investment	(162,908)	(107,641)	(73,812)
Loss on equity method investment	(1,010)	—	—
Net loss	$ (163,918)	$ (107,641)	$ (73,812)
Net loss per share:			
Net loss per share - basic and diluted	$ (3.15)	$ (2.80)	$ (2.42)
Weighted average shares - basic and diluted	51,982	38,436	30,448
Other comprehensive income (loss):			
Unrealized loss on investment securities	$ (3,549)	$ (407)	$ (123)
Comprehensive loss	$ (167,467)	$ (108,048)	$ (73,935)

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS, INC.

Consolidated Statements of Stockholders' Equity
(in thousands)

	Common Stock Shares	Common Stock and Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
Balance at January 1, 2020	24,263	$ 210,793	$ 148	$ (93,802)	$ 117,139
Issuance of common stock, net of $7.5 million of transaction costs	8,499	114,283	—	—	114,283
Vesting of shares subject to repurchase	17	26	—	—	26
Exercise of stock options	171	288	—	—	288
Stock issued under Stock Purchase Plan	51	691	—	—	691
Stock-based compensation	—	10,427	—	—	10,427
Comprehensive loss	—	—	(123)	—	(123)
Net loss	—	—	—	(73,812)	(73,812)
Balance at December 31, 2020	33,001	336,508	25	(167,614)	168,919
Issuance of common stock, net of $12.9 million of transaction costs	14,126	249,542	—	—	249,542
Vesting of shares subject to repurchase	15	21	—	—	21
Exercise of stock options	364	3,137	—	—	3,137
Stock issued under Stock Purchase Plan	91	1,021	—	—	1,021
Stock-based compensation	—	17,352	—	—	17,352
Comprehensive loss	—	—	(407)	—	(407)
Net loss	—	—	—	(107,641)	(107,641)
Balance at December 31, 2021	47,597	607,581	(382)	(275,255)	331,944
Issuance of common stock, net of $7.8 million transaction costs	5,626	117,242	—	—	117,242
Vesting of shares subject to repurchase	1	2	—	—	2
Exercise of stock options	524	4,721	—	—	4,721
Stock issued under Stock Purchase Plan	129	1,618	—	—	1,618
Stock-based compensation	—	28,268	—	—	28,268
Comprehensive loss	—	—	(3,549)	—	(3,549)
Net loss	—	—	—	(163,918)	(163,918)
Balance at December 31, 2022	53,877	$ 759,432	$ (3,931)	$ (439,173)	$ 316,328

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows
(In thousands)

	Year ended December 31,		
	2022	2021	2020
Operating activities:			
Net loss	$ (163,918)	$ (107,641)	$ (73,812)
Reconciliation of net loss to net cash used in operating activities:			
Stock-based compensation	28,268	17,352	10,427
Depreciation and amortization	983	922	948
Noncash lease expense	406	340	278
Accretion of purchase discounts and amortization of premiums on investment securities, net	34	422	(227)
Noncash license revenues	—	(1,078)	—
Loss on equity method investment	1,010	—	—
Change in fair value of derivative asset	(600)	—	—
Other, net	—	(1)	(17)
Increase (decrease) in cash resulting from changes in:			
Prepaid expenses and other assets	215	(4,361)	(1,623)
Accounts payable and accrued expenses, compensation and related expenses	10,994	6,293	2,723
Deferred revenue	8,341	—	—
Operating lease liability	(938)	(836)	(724)
Net cash used in operating activities	(115,205)	(88,588)	(62,027)
Investing activities:			
Purchases of investment securities	(329,817)	(125,404)	(135,592)
Maturities of investment securities	157,493	69,357	135,995
Purchases of property and equipment	(1,656)	(436)	(186)
Net cash (used in) provided by investing activities	(173,980)	(56,483)	217
Financing activities:			
Proceeds from issuance of common stock, net of $7.8 million (2022), $12.9 million (2021) and $7.5 million (2020) transaction costs	117,242	249,542	114,283
Proceeds from exercise of stock options	4,721	3,137	288
Net cash provided by financing activities	121,963	252,679	114,571
Net change in cash, cash equivalents and restricted cash	(167,222)	107,608	52,761
Cash, cash equivalents and restricted cash - beginning of period	201,195	93,587	40,826
Cash, cash equivalents and restricted cash - end of period	$ 33,973	$ 201,195	$ 93,587
Components of cash, cash equivalents and restricted cash:			
Cash and cash equivalents	$ 32,672	$ 200,695	$ 93,087
Restricted cash	1,301	500	500
Cash, cash equivalents and restricted cash at end of period	$ 33,973	$ 201,195	$ 93,587
Non-cash activity:			
Investment in Radionetics	$ —	$ 1,010	$ —
Derivative asset	$ —	$ 68	$ —
Stock issued under Stock Purchase Plan	$ 1,618	$ 1,021	$ 691
Amounts accrued for purchases of property and equipment	$ —	$ 130	$ 6
Change in unvested stock liability	$ 2	$ 21	$ 26

See the accompanying notes to these consolidated financial statements.

1. ORGANIZATION AND BASIS OF PRESENTATION

Description of Business

Crinetics Pharmaceuticals, Inc. (the "Company") is a clinical-stage pharmaceutical company incorporated in Delaware on November 18, 2008 and based in San Diego, California. The Company is focused on the discovery, development and commercialization of novel therapeutics for rare endocrine diseases and endocrine-related tumors. In January 2017, the Company established a wholly-owned Australian subsidiary, Crinetics Australia Pty Ltd ("CAPL"), in order to conduct various preclinical and clinical activities for its development candidates.

Principles of Consolidation and Foreign Currency Transactions

The consolidated financial statements include the accounts of the Company and CAPL. All intercompany accounts and transactions have been eliminated in consolidation. The functional currency of both the Company and CAPL is the U.S. dollar. Assets and liabilities that are not denominated in the functional currency are remeasured into U.S. dollars at foreign currency exchange rates in effect at the balance sheet date except for nonmonetary assets, which are remeasured at historical foreign currency exchange rates in effect at the date of transaction. Net realized and unrealized gains and losses from foreign currency transactions and remeasurement are reported in other income (expense), in the accompanying consolidated statements of operations and comprehensive loss and were not material for all periods presented.

Segment Reporting

Operating segments are identified as components of an enterprise about which discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business in one operating segment.

Liquidity

From inception, the Company has devoted substantially all of its efforts to drug discovery and development and conducting preclinical studies and clinical trials. The Company has a limited operating history and the sales and income potential of the Company's business and market are unproven. Successful transition to attaining profitable operations is dependent upon achieving a level of revenues adequate to support the Company's cost structure. The Company has experienced net losses and negative cash flows from operating activities since its inception and has an accumulated deficit of $439.2 million as of December 31, 2022.

As of December 31, 2022, the Company had $334.4 million in unrestricted cash, cash equivalents and investment securities. To date, the Company has been funded primarily through equity offerings. On August 13, 2019, the Company entered into a sales agreement and prospectus supplement filed on August 12, 2022, whereby the Company may offer and sell shares of its common stock from time to time up to $150.0 million through the sales agents (the "ATM Offering"). As of December 31, 2022, 275,764 shares had been sold through the ATM Offering, for net proceeds of $6.4 million, after deducting commissions of $0.2 million, (see Note 9).

The Company expects to continue to incur net losses for the foreseeable future and believes it will need to raise substantial additional capital to accomplish its business plan over the next several years. The Company plans to continue to fund its losses from operations and capital funding needs through a combination of equity offerings, debt financings or other sources, including potential collaborations, licenses and other similar arrangements. If the Company is not able to secure adequate additional funding, the Company may be forced to make reductions in spending, extend payment terms with suppliers, liquidate assets where possible, or suspend or curtail planned programs. Any of these actions could materially harm the Company's business, results of operations and future prospects. There can be no assurance as to the availability or terms upon which such financing and capital might be available in the future.

COVID-19

The extent of the impact of COVID-19 on the Company's operational and financial performance will depend on certain developments, which are highly uncertain and cannot be predicted with confidence. The Company continues to actively monitor COVID-19 and may take further actions that alter its operations, including those that may be required by federal, state or local authorities, or that the Company determines are in the best interests of its employees and other third parties with whom the Company does business. For example, the recent lifting of COVID-19 restrictions and subsequent COVID-19 outbreaks in China have delayed the Company's planned recruitment of patients in our PATHFNDR-2 study. While COVID-19 has not had a material effect on the Company's financial results, the degree to which COVID-19 or an outbreak of another highly infectious or contagious disease may impact the Company's future financial condition or results of operations is

uncertain, and the Company may continue to experience disruptions that could impact its business, drug manufacturing, nonclinical activities, and clinical trials.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Use of Estimates

The Company's consolidated financial statements are prepared in accordance with U.S. generally accepted accounting principles ("U.S. GAAP"). The preparation of the Company's consolidated financial statements requires it to make estimates and assumptions that impact the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in the Company's consolidated financial statements and accompanying notes. The most significant estimates in the Company's consolidated financial statements relate to accrual of research and development expenses, valuation of stock-based awards, fair values of financial instruments, revenue recognition, and investment in Radionetics. Estimates are based on historical experiences or on forecasts, including information received from third parties and various other factors that the Company believes are reasonable under the circumstances. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from those estimates.

Investment in Radionetics

The Company first analyzes its investment in another entity to determine if the entity is a variable interest entity ("VIE") and if so, whether the Company is the primary beneficiary requiring consolidation. An entity is considered a VIE if (1) the entity does not have enough equity to finance its own activities without additional support, (2) the entity's at-risk equity holders lack the characteristics of a controlling financial interest, or (3) the entity is structured with non-substantive voting rights. VIEs are consolidated by the primary beneficiary, which is the entity that has both the power to direct the activities that most significantly impact the VIE's economic performance and the obligation to absorb losses or the right to receive benefits from the VIE that potentially could be significant to the VIE. Variable interests in a VIE can be contractual, ownership, or other financial interests. The Company re-assesses its investment upon reconsideration events to determine whether the Company is the primary beneficiary of the VIE, in which case the Company would consolidate the VIE.

If it has been determined that the Company is not the primary beneficiary or does not have control but does have the ability to exercise significant influence over the VIE, the Company accounts for the unconsolidated investment under the equity method of accounting.

As discussed in Note 8, in October 2021, the Company, together with 5AM Ventures ("5AM") and Frazier Healthcare Partners ("Frazier"), announced the formation of Radionetics Oncology, Inc. ("Radionetics"). Radionetics aims to develop a deep pipeline of novel, targeted, nonpeptide radiopharmaceuticals for the treatment of a broad range of oncology indications. Radionetics is a VIE. The Company maintains an equity interest in Radionetics and accounts for its investment in Radionetics under the equity method of accounting. The Company records its share of Radionetics income (loss) outside of operations in the statements of operations and comprehensive loss on a quarterly lag. Since the Company's investment in Radionetics was obtained on October 15, 2021, the Company recorded its share of income (loss) beginning in the first quarter of 2022. The Company's equity method investment in Radionetics was written down to zero during the first quarter of 2022 as a result of the allocation of the Company's share of losses of the investee.

Fair Value Measurements

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or non-recurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1: Observable inputs such as quoted prices in active markets.

Level 2: Inputs, other than the quoted prices in active markets, that are observable either directly or indirectly.

Level 3: Unobservable inputs in which there is little or no market data, which require the reporting entity to develop its own assumptions about risk and the assumptions market participants would use in pricing the asset or liability developed based on the best information available in the circumstances.

The carrying amounts of the Company's current financial assets, restricted cash and current financial liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments. The Company recorded the derivative asset (see Note 8) and investment securities (see Note 3) at fair value.

Cash, Cash Equivalents and Restricted Cash

Cash and cash equivalents include cash held in readily available checking and money market accounts, as well as short-term debt securities with maturities of three months or less when purchased. Restricted cash represents cash held as collateral for the Company's facility leases and is reported as a long-term asset in the accompanying consolidated balance sheets.

Investment Securities

All investments have been classified as "available-for-sale" and are carried at fair value as determined based upon quoted market prices or pricing models for similar securities at period end. Investments with contractual maturities less than 12 months at the balance sheet date are considered short-term investments. Investments with contractual maturities beyond one year are also classified as short-term due to the Company's ability to liquidate the investment for use in operations within the next 12 months.

Realized gains and losses on investment securities are derived using the specific identification method for determining the cost of securities sold and are included in other income (expenses), net in the accompanying consolidated statements of operations and comprehensive loss. The Company has not realized any significant gains or losses on sales of available-for-sale investment securities during any of the periods presented. All of the Company's investment holdings are in the form of debt securities, therefore unrealized gains and losses that are determined to be temporary in nature are reported as a component of accumulated other comprehensive income. Investment securities are evaluated periodically for impairment. A decline in the fair value of any security below cost that is deemed other than temporary results in a charge to earnings and the establishment of a new cost basis for the security. Interest income is recognized when earned and is included in interest income in the accompanying consolidated statements of operations and comprehensive loss, as are the amortization of purchase premiums and accretion of purchase discounts on investment securities.

Derivative Asset

Derivatives are recorded at fair value and changes in fair value are recorded through the statements of operations and comprehensive loss each period. The Company has a single derivative instrument, a warrant (the "Radionetics Warrant") received on October 15, 2021, to purchase the greater of 3,407,285 additional shares of common stock or the number of additional shares of common stock that would allow the Company to maintain an aggregate equity interest of 22% of the fully diluted capitalization of Radionetics, a private company. The Company records the Radionetics Warrant as long-term on the balance sheets due to the lack of marketability, such that it is not expected to be available for current operations. Changes in fair value of the Radionetics Warrant are recognized in other income (expense) in the accompanying consolidated statements of operations and comprehensive loss.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash, cash equivalents and investment securities. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and believes it is not exposed to significant risk on its cash balances due to the financial position of the depository institution in which those deposits are held. Additionally, the Company has established guidelines regarding approved investments and maturities of investments, which are designed to maintain safety and liquidity.

Leases

The Company determines if an arrangement is a lease at the inception of the arrangement. Leases with a term longer than 12 months that are determined to be operating leases are included in operating lease right-of-use assets, other current liabilities and noncurrent operating lease liabilities in the consolidated balance sheets at the commencement date of the arrangement. The Company accounts for each separate lease and non-lease component as a single lease component. When the Company's leases do not provide an implicit rate, an incremental borrowing rate is used based on the information available at commencement dates in determining the present value of lease payments. The incremental borrowing rate is the rate of interest that the Company would expect to pay to borrow over a similar term, and on a collateralized basis, an amount equal to the lease payments in a similar economic environment. The Company's lease terms may include options to extend or terminate the lease when the Company is reasonably certain that it will exercise such options. Lease expense for lease payments is recognized on a straight-line basis over the lease term. Lease agreements may contain variable costs such as common area maintenance, insurance, taxes or other costs. Such variable lease costs are expensed as incurred. Lease expense for lease payments is recognized on a straight-line basis over the lease term. The Company assesses its leases to determine whether the arrangements contain lease incentives.

Property and Equipment, Net

Property and equipment consist of leasehold improvements, and lab and various other equipment. Such assets are stated at cost and depreciated on a straight-line basis over the estimated useful life of the related assets. The Company estimates its useful lives of its lab and other equipment as follows: lab equipment – three to five years; office equipment - three to five years; computer and software – three years. Leasehold improvements are amortized over the estimated useful life of the improvement or the remaining term of the associated lease.

Repairs and maintenance costs are charged to expense as incurred and expenditures that materially extend the useful lives of assets are capitalized.

Impairment of Long-Lived Assets

The Company reviews long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of the assets (or asset group) may not be fully recoverable.

Factors considered in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in the use of the assets. An impairment loss is recognized when estimated undiscounted future cash flows expected to result from the use of an asset (or asset group) are less than its carrying amount. If such assets are considered impaired, the impairment loss recognized is measured as the excess of the carrying value of the impaired asset over its fair value, determined based on future cash flows or appraised values, depending on the nature of the asset (or asset group). The Company has not recognized any impairment losses in any of the periods presented in these consolidated financial statements.

Revenue Recognition

The Company has generated revenue from licensing and supply agreement arrangements. The Company recognizes revenues when, or as, the promised goods or services are transferred to customers in an amount that reflects the consideration to which it expects to be entitled in exchange for those services. To determine revenue recognition for arrangements, the Company performs the following five steps: (1) identify the contract(s) with a customer; (2) identify the performance obligation(s) in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligation(s) in the contract; and (5) recognize revenue when (or as) the performance obligation(s) are satisfied. At contract inception, the Company assesses the goods or services promised within each contract, assesses whether each promised good or service is distinct and identifies those that are performance obligations. The Company recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when, or as, the performance obligation is satisfied.

The Company has entered into licensing and collaboration agreements that mainly include the following: (i) upfront considerations; (ii) payments associated with achieving certain milestones; and (iii) royalties based on specified percentages of net product sales, if any.

The Company has also entered into a manufacturing and supply arrangement that includes reimbursements of costs plus a pre-determined margin.

At the initiation of an agreement, the Company analyzes each unit of account within the contract to determine if the counterparty is a customer in the context of the unit of account.

The Company considers a variety of factors in determining the appropriate estimates and assumptions under the arrangements, such as whether the elements are distinct performance obligations, whether there are observable standalone prices, whether the license is functional or symbolic, and whether the Company is acting as the agent or principal. The Company evaluates each performance obligation to determine if it can be satisfied and recognized as revenue at a point in time or over time.

At the inception of arrangements that include variable consideration, the Company uses judgment to estimate the amount of variable consideration to include in the transaction price using the most likely method. If it is probable that a significant revenue reversal will not occur, then the estimated amount is included in the transaction price. Milestone payments that are not within the Company's or the licensee’s control, such as regulatory approvals, are not included in the transaction price until those approvals are received. At the end of each reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint and, as necessary, adjusts the estimate of the overall transaction price. Any adjustments will be recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

The Company develops estimates of the standalone selling price for each distinct performance obligation. Variable consideration that relates specifically to efforts to satisfy specific performance obligations is allocated entirely to those

performance obligations. Other components of the transaction price are allocated based on the relative standalone selling price, over which management has applied significant judgment. The Company determines the standalone selling price for license-related performance obligations using a market approach, which may include assumptions such as forecasted revenues, development timelines, discount rates and probabilities of success. The Company estimates the standalone selling price for the data exchange performance obligation (see Note 8) by forecasting the expected costs of satisfying a performance obligation plus a predetermined margin.

In the case of a license that is a distinct performance obligation, the Company recognizes revenue allocated to the license from non-refundable, up-front fees at the point in time when the license is transferred to the licensee and the licensee can use and benefit from the license. For licenses that are bundled with other distinct or combined obligations, the Company uses judgment to assess the nature of the performance obligation to determine whether the performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. If the performance obligation is satisfied over time, then the Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

The selection of the method to measure progress towards completion requires judgment and is based on the nature of the products or services to be provided. The Company has used the cost-to-cost measure of progress because it best depicts the transfer of control to the customer which occurs as the Company incurs costs. Under the cost-to-cost measure of progress, the extent of progress towards completion is measured based on the ratio of costs incurred to date to the total estimated costs at completion of the performance obligation, which is considered an input method. The Company uses judgment to estimate the total cost of these over time performance obligations, which include subcontractors' costs, labor, materials, other direct costs and an allocation of indirect costs. The Company evaluates these cost estimates and the progress each reporting period and, as necessary, the Company adjusts the measure of progress and related revenue recognition.

Sales-based milestones and royalties are recognized at the later of when the subsequent sale or usage occurs or the performance obligation for which some or all of the sales-based milestones and royalties have been allocated to has been satisfied or partially satisfied.

The Company's grant revenues are derived from Small Business Innovation Research Grants ("SBIR Grants") from the National Institutes of Health. The Company's performance obligation under SBIR Grants consists of research activities and the Company recognizes SBIR Grant revenue over time as reimbursable grant costs are incurred up to pre-approved award limits within the budget period. The costs associated with these reimbursements are reflected as a component of research and development expense in the accompanying consolidated statements of operations and comprehensive loss. Earnings in excess of billings are included as a component of prepaid expenses and other current assets in the accompanying consolidated balance sheets.

Research and Development Expenses

Research and development ("R&D") expenses consist primarily of salaries, payroll taxes, employee benefits and stock-based compensation for individuals involved in R&D efforts, as well as consulting expenses, third-party R&D expenses, laboratory supplies, clinical materials and overhead, including facilities and depreciation costs, offset by the Australian Tax Incentive discussed below. R&D expenses are charged to expense as incurred. Payments made prior to the receipt of goods or services to be used in R&D are capitalized until the goods or services are received and are recorded as prepaid expenses and other current assets. Costs incurred under contracts with contract research organizations that conduct and manage the Company's clinical trials are also included in R&D expenses. The financial terms and activities of these agreements vary from contract to contract and may result in uneven expense levels. Generally, these agreements set forth activities that drive the recording of expenses such as start-up and initiation activities, enrollment and treatment of patients, or the completion of other clinical trial activities. Expenses related to clinical trials are accrued based on estimates and/or representations from service providers regarding work performed, including actual level of patient enrollment, completion of patient studies and progress of the clinical trials. Other incidental costs related to patient enrollment or treatment are accrued when reasonably certain. If the amounts that the Company is obligated to pay under its clinical trial agreements are modified (for instance, as a result of changes in the clinical trial protocol or scope of work to be performed), the Company adjusts its accruals accordingly on a prospective basis. Revisions to contractual payment obligations are charged to expense in the period in which the facts that give rise to the revision become reasonably certain.

Australian Tax Incentive

CAPL is eligible to obtain a cash refund from the Australian Taxation Office for eligible R&D expenditures under the Australian R&D Tax Incentive Program (the "Australian Tax Incentive"). The Australian Tax Incentive is recognized as a reduction to R&D expense when there is reasonable assurance that the relevant expenditure has been incurred, the amount can be reliably measured and that the Australian Tax Incentive will be received. The Company recognized reductions to R&D expense of $0.8 million, $0.3 million and $0.6 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Patent Costs

All costs incurred for the filing of patent applications are recorded as general and administrative expenses in the accompanying consolidated statements of operations and comprehensive loss when incurred, as the recoverability of these expenses is uncertain.

Stock-Based Compensation

Stock-based compensation expense represents the estimated grant date fair value of the Company's equity awards, consisting of stock options, restricted stock units and shares issued under the Company's Employee Stock Purchase Plan, recognized over the requisite service period of such awards (usually the vesting period) on a straight-line basis. The Company estimates the fair value of all stock option grants using the Black-Scholes option pricing model and recognizes forfeitures as they occur. Restricted stock units are valued using the grant date stock price. For stock awards for which vesting is subject to performance-based milestones, the expense is recorded over the remaining service period after the point when the achievement of the milestone is probable, or the performance condition has been achieved.

Income Taxes

The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the consolidated financial statements. Under this method, deferred tax assets and liabilities are determined based on the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in income in the period that includes the enactment date.

The Company recognizes net deferred tax assets to the extent that the Company believes these assets are more likely than not to be realized. In making such a determination, management considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies, and results of recent operations. If management determines that the Company would be able to realize its deferred tax assets in the future in excess of their net recorded amount, management would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

The Company records uncertain tax positions on the basis of a two-step process whereby (1) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority. The Company recognizes interest and penalties related to unrecognized tax benefits within income tax expense, and any accrued interest and penalties would be included within the related tax liability. No such costs were recorded during the three years ended December 31, 2022.

Comprehensive Loss

Comprehensive loss is comprised of the Company's net loss and the unrealized gains or losses on the Company's available for sale investment securities for all periods presented. The cumulative amount of unrealized gains and losses is reflected as a separate component of stockholders' equity in the accompanying consolidated balance sheets as accumulated other comprehensive income (loss). There are no tax effects for the years ended December 31, 2022, 2021 and 2020.

Net Loss Per Share

Basic net loss per share is computed by dividing the net loss by the weighted-average number of common shares outstanding for the period, without consideration for potentially dilutive securities. Diluted net loss per share is computed by dividing the net loss by the weighted-average number of shares of common stock and dilutive common stock equivalents outstanding for the period determined using the treasury-stock. Dilutive common stock equivalents are comprised of common stock subject to repurchase, and options outstanding under the Company's stock option plan. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding as inclusion of the potentially dilutive securities on loss per share would be antidilutive.

Potentially dilutive securities (in common stock equivalent shares) not included in the calculation of diluted net loss per share because to do so would be anti-dilutive are as follows (*in thousands*):

	Year ended December 31,		
	2022	2021	2020
Stock options	9,757	6,554	4,422
Restricted stock units	290	—	—
Employee stock purchase plan	282	207	183
Unvested common stock subject to repurchase	—	1	16
Total	10,329	6,762	4,621

Recently Adopted Accounting Pronouncements

ASU 2021-04

In May 2021, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2021-04, *Earnings Per Share* ("Topic 260"), *Debt-Modifications and Extinguishments* ("Subtopic 470-50"), *Compensation-Stock Compensation* ("Topic 718"), and *Derivatives and Hedging-Contracts in Entity's Own Equity* ("Subtopic 815-40"): *Issuer's Accounting for Certain Modifications or Exchanges of Freestanding Equity-Classified Written Call Options* ("ASU 2021-04"), which intends to clarify and reduce diversity in an issuer's accounting for modifications or exchanges of freestanding equity-classified written call options (for example, warrants) that remain equity classified after modification or exchange. The Company adopted ASU 2021-04 as of January 1, 2022, which did not have an impact on its consolidated financial statements.

Recent Accounting Pronouncements

ASU 2016-13

In June 2016, the FASB issued ASU No. 2016-13, "Financial Instruments - Credit Losses (Topic 326): *Measurement of Credit Losses on Financial Instruments*" ("Topic 326"). Topic 326 amends guidance on reporting credit losses for assets held at amortized cost basis and available for sale debt securities. For assets held at amortized cost basis, Topic 326 eliminates the probable initial recognition threshold in current GAAP and, instead, requires an entity to reflect its current estimate of all expected credit losses. The allowance for credit losses is a valuation account that is deducted from the amortized cost basis of the financial assets to present the net amount expected to be collected. For available for sale debt securities, credit losses should be measured in a manner similar to current GAAP, however Topic 326 will require that credit losses be presented as an allowance rather than as a write-down. This ASU update affects entities holding financial assets and net investment in leases that are not accounted for at fair value through net income. This update is effective for the Company for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. The Company adopted ASU 2016-13 as of January 1, 2023, which did not have a material impact on the consolidated financial statements.

3. INVESTMENT SECURITIES

The Company reports its available-for-sale investment securities at their estimated fair values. Available-for-sale investment securities consisted of the following as of December 31, 2022 and 2021 (*in thousands*):

	As of December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Market Value
Available-for-sale investment securities:				
U.S. government and agency obligations	$ 154,228	$ 12	$ (1,510)	$ 152,730
Certificates of deposit	4,629	—	(94)	4,535
Corporate debt securities	145,330	—	(2,336)	142,994
Asset-backed securities	1,497	—	(3)	1,494
Total	$ 305,684	$ 12	$ (3,943)	$ 301,753

	As of December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Market Value
Available-for-sale investment securities:				
U.S. government and agency obligations	$ 54,637	$ —	$ (180)	54,457
Certificates of deposit	5,735	1	(4)	5,732
Corporate debt securities	70,600	6	(204)	70,402
Asset-backed securities	2,421	—	—	2,421
Total	$ 133,393	$ 7	$ (388)	$ 133,012

As of December 31, 2022 and 2021, available-for-sale investment securities by contractual maturity were as follows (*in thousands*):

	As of December 31, 2022		As of December 31, 2021	
	Amortized Cost	Fair Market Value	Amortized Cost	Fair Market Value
Available-for-sale investment securities:				
Due in one year or less	$ 246,276	$ 243,542	$ 31,101	$ 31,078
Due after one year through five years	59,408	58,211	102,292	101,934
Total	$ 305,684	$ 301,753	$ 133,393	$ 133,012

As of December 31, 2022, available-for-sale investment securities by length of time in a net loss position were as follows (*in thousands*):

	As of December 31, 2022					
	Less Than 12 Months		More Than 12 Months		Total	
	Fair Market Value	Gross Unrealized Losses	Fair Market Value	Gross Unrealized Losses	Fair Market Value	Gross Unrealized Losses
Available-for-sale investment securities:						
U.S. government and agency obligations	$ 95,933	$ (702)	$ 36,681	$ (808)	$ 132,614	$ (1,510)
Certificates of deposit	2,399	(47)	2,136	(47)	4,535	(94)
Corporate debt securities	96,663	(1,399)	43,330	(937)	139,993	(2,336)
Asset-backed securities	1,494	(3)	—	—	1,494	(3)
Total	$ 196,489	$ (2,151)	$ 82,147	$ (1,792)	$ 278,636	$ (3,943)

As of December 31, 2021, there were no available-for-sale investment securities at a loss position for a period of twelve months or more. The Company reviewed its investment holdings as of December 31, 2022 and 2021 and determined that its unrealized losses were not considered to be other-than-temporary based upon (i) the financial strength of the issuing institution, (ii) intent and ability of the securities to be held to maturity and (iii) the fact that the Company is expected to recover the amortized cost of its investment holdings. As such, the Company has not recognized any impairment in its financial statements related to its available-for-sale investment securities. During the years ended December 31, 2022, 2021, and 2020, the Company recognized ($86,000), $2,000 and $26,000, respectively, of realized net gains (losses) in the accompanying statements of operations and comprehensive loss.

4. FAIR VALUE MEASUREMENTS

Investment Securities

The Company holds investment securities that consist of highly liquid, investment grade debt securities. The Company determines the fair value of its investment securities based upon one or more valuations reported by its investment accounting and reporting service provider. The investment service provider values the securities using a hierarchical security pricing model that relies primarily on valuations provided by an industry-recognized valuation service. Such valuations may be based on trade prices in active markets for identical assets or liabilities (Level 1 inputs) or valuation models using inputs that are observable either directly or indirectly (Level 2 inputs), such as quoted prices for similar assets or liabilities, yield curves, volatility factors, credit spreads, default rates, loss severity, current market and contractual prices for the underlying instruments or debt, and broker and dealer quotes, as well as other relevant economic measures.

Derivative Asset

On October 15, 2021, the Company received the Radionetics Warrant to purchase the greater of 3,407,285 additional shares of common stock or the number of additional shares of common stock that would allow the Company to maintain an aggregate equity interest of 22% of the fully diluted capitalization of Radionetics. The valuation method and primary inputs used in valuing the Radionetics Warrant are discussed in Note 8. Such valuation is based on valuations provided by a third-party valuation specialist using unobservable inputs due to little to no market data (Level 3 inputs). During the year ended December 31, 2022, the Company recorded $0.6 million of income in the accompanying consolidated statements of operations and comprehensive loss related to the change in value of the Radionetics Warrant.

Financial assets measured at fair value on a recurring basis as of December 31, 2022 and 2021 were as follows (in thousands):

	As of December 31, 2022			
	Level 1	Level 2	Level 3	Total
Investment securities:				
U.S. government and agency obligations	$ 93,879	$ 58,851	$ —	$ 152,730
Certificates of deposit	—	4,535	—	4,535
Corporate debt securities	—	142,994	—	142,994
Asset-backed securities	—	1,494	—	1,494
Total Investment securities	93,879	207,874	—	301,753
Derivative Assets:				
Radionetics Warrant	—	—	668	668
Total assets measured at fair value	$ 93,879	$ 207,874	$ 668	$ 302,421

	As of December 31, 2021			
	Level 1	Level 2	Level 3	Total
Investment securities:				
U.S. government and agency obligations	$ 44,984	$ 9,473	$ —	$ 54,457
Certificates of deposit	—	5,732	—	5,732
Corporate debt securities	—	70,402	—	70,402
Asset-backed securities	—	2,421	—	2,421
Total Investment securities	44,984	88,028	—	133,012
Derivative Assets:				
Radionetics Warrant	—	—	68	68
Total assets measured at fair value	$ 44,984	$ 88,028	$ 68	$ 133,080

The Company's policy is to recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer. There were no transfers into or out of Level 3 during the years ended December 31, 2022 and 2021.

5. BALANCE SHEET DETAILS

Prepaid expenses and other current assets consisted of the following (*in thousands*):

	December 31, 2022	December 31, 2021
Prepaid clinical costs	$ 2,567	$ 6,313
Prepaid research and development costs	2,293	$ 871
Australian tax incentive receivable	937	977
Prepaid insurance	939	888
Interest receivable	1,353	499
Due from Radionetics (Note 8)	135	553
Other	2,535	912
Total	$ 10,759	$ 11,013

Property and equipment, net consisted of the following (*in thousands*):

	December 31, 2022	December 31, 2021
Leasehold improvements	$ 3,516	$ 3,516
Lab equipment	3,168	1,889
Office equipment	859	859
Computers and software	41	41
Property and equipment at cost	7,584	6,305
Less accumulated depreciation and amortization	(4,084)	(3,480)
Total	$ 3,500	$ 2,825

Depreciation and amortization expense was $1.0 million, $0.9 million and $0.9 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Accounts payable and accrued expenses consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Accounts payable	$ 6,883	$ 3,422
Accrued clinical costs	1,921	1,095
Accrued research and development costs	4,043	3,091
Accrued outside services and professional fees	1,810	537
Other accrued expenses	694	323
Total	$ 15,351	$ 8,468

6. OPERATING LEASE

In February 2018, as amended in March 2018, the Company entered into a non-cancelable operating lease for a facility in San Diego, California (the "2018 Lease"). The 2018 Lease has an initial term of seven years which expires in August 2025, and the Company has an option to extend the term of the 2018 Lease for an additional five years, a termination option subject to early termination fees and an option to sublease the facility. The 2018 Lease is subject to base lease payments and additional charges for common area maintenance and other costs and includes certain lease incentives and tenant improvement allowances. The Company's estimated incremental fully collateralized borrowing rate of 8.0% was used in its present value calculation as the 2018 Lease does not have a stated rate and the implicit rate was not readily determinable.

On September 9, 2022, the Company entered into a lease agreement for laboratory and office space in San Diego, California (the "2022 Lease"). The Company expects to move its corporate headquarters to this new facility in the second half of 2023 upon the substantial completion of improvements.

Under the terms of the 2022 Lease, the Company's expected future monthly minimum lease payments of $0.5 million, with six months of rent abatement in the first year, start on the earlier of (i) the date which is ten (10) months after substantial completion of demolition work, or (ii) the date of the substantial completion of improvements and first occupancy for business purposes, and the term expires on the date immediately preceding the one hundred thirty-seventh (137th) monthly anniversary of this lease payment start date. Lease payments are subject to annual 3% increases. The Company is also responsible for certain operating expenses and taxes during the term of the 2022 Lease. The 2022 Lease provides the Company with specified tenant improvement and landlord work allowances. The Company has (i) two options to extend the term of the 2022 Lease for an additional period of five (5) years each, and (ii) a right of first offer on adjacent space to the new facility, subject to the terms and conditions of the 2022 Lease. As of December 31, 2022, the 2022 Lease did not commence because the construction of improvements to bring the facility to its intended use was ongoing and not substantially complete.

Under the terms of the 2018 Lease and 2022 Lease, the Company provided the lessors with irrevocable letters of credit in the amounts of $0.5 million and $0.8 million, respectively. The lessors are entitled to draw on the letters of credit in the event of any default by the Company under the terms of the leases.

As of December 31, 2022, future minimum payments under non-cancellable operating leases were as follows (*in thousands*):

Year ending December 31,	Minimum Payments
2023	$ 1,244
2024	1,280
2025	871
Total future minimum lease payments	3,395
Less imputed interest	(320)
Total operating lease liabilities	3,075
Less operating lease liabilities, current	(1,051)
Operating lease liabilities, non-current	$ 2,024

Operating lease cost was $1.0 million for each of the years ended December 31, 2022, 2021 and 2020. As of December 31, 2022 and 2021, the Company's operating lease weighted average remaining term was 2.6 years and 3.6 years, respectively. As of December 31, 2022 and 2021, the Company's weighted-average discount rate was 8%.

Cash paid for amounts included in the measurement of lease liabilities for operating cash flow from operating leases was $1.2 million, $1.2 million, and $1.1 million during each of the years ended years ended December 31, 2022, 2021 and 2020.

7. COMMITMENTS AND CONTINGENCIES

Litigation

From time to time, the Company may be subject to various claims and suits arising in the ordinary course of business. The Company does not expect that the resolution of these matters will have a material adverse effect on its financial position or results of operations.

8. REVENUE RECOGNITION

Radionetics Oncology, Inc.

Formation

In October 2021, the Company, together with 5AM and Frazier, announced the formation of Radionetics. Radionetics aims to develop a deep pipeline of novel, targeted, nonpeptide radiopharmaceuticals for the treatment of a broad range of oncology indications.

The Radionetics License

The Company and Radionetics entered into the collaboration and license agreement (the "Radionetics License"), under which the Company granted to Radionetics an exclusive world-wide license to its radiotherapeutics technology platform and associated intellectual property for use in developing radiotherapeutics and related radio-imaging agents, including exclusive rights to the underlying intellectual property on certain preclinical drug candidates. Under the Radionetics License, the Company will not be supporting or maintaining the intellectual property and does not plan on continuing to undertake those activities from which the utility of the intellectual property is derived. The collaborative provisions per the Radionetics License are deemed to be protective measures for the advancement of the technology and not deemed to be a separate performance obligation. The Company assessed the Radionetics License and concluded that Radionetics is a customer within the Radionetics License. The performance obligation under the Radionetics License consisted of the license and know-how of the technology that was transferred at the inception of the Radionetics License.

In exchange, the Company received 50,500,000 shares of common stock of Radionetics, which represents an initial majority stake in Radionetics of 64%, and the Radionetics Warrant to purchase the greater of 3,407,285 additional shares of common stock or the number of additional shares of common stock that would allow the Company to maintain an aggregate equity interest of 22% of the fully diluted capitalization of Radionetics. The exercise price of the Radionetics Warrant is $0.00001 and it is exercisable at any time and has a term of 10 years. As of December 31, 2022, the Company had a 56% ownership stake in Radionetics.

The upfront noncash consideration was valued at $1.1 million, which was comprised of $1.0 million for the Company's share of Radionetics common stock and $0.1 million for the Radionetics Warrant. The Radionetics License is for functional intellectual property which was transferred at the inception of the Radionetics License. The Company does not have an ongoing performance obligation to support or maintain the licensed intellectual property under the Radionetics License. In October 2021, the entire amount of the upfront noncash consideration of $1.1 million was recognized as license revenue upon the Company's transfer of the license under the Radionetics License.

In addition to the upfront non-cash considerations, the Company may receive potential sales milestones in excess of $1.0 billion and single-digit royalties on net sales. As there have been no sales to date, no sales-based milestones or royalties were recognized to date.

Valuation of Upfront Noncash Considerations

The Company engaged a third-party valuation specialist to assist the Company with its determination of the estimated fair value of these upfront noncash considerations received. The valuation specialist utilized a cost approach to determine the implied value of Radionetics' equity since it was newly formed with early development stage technology from the Radionetics License for which there are not reliable long-term forecasts. Next, the total equity value was allocated to various share classes using the current value method and option pricing method. The current value method allocates the value of the business to the shareholders' given consideration of senior obligations such as debt, equity certificates and other preferred equity. The option pricing method entails allocating the total shareholders' equity value to the various share classes based upon their respective claims on a series of call options with strike prices at various value levels depending upon the rights and preferences of each class.

The primary inputs used in valuing the Radionetics common stock and the Radionetics Warrant, were as follows:

Derivative Asset	December 31, 2022	October 15, 2021 and December 31, 2021
Expected term	1.8 years	3.0 years
Expected volatility	116.6%	111.4%
Risk free interest rate	4.5%	0.7%
Marketability discount	51.0%	30.0%

The Company estimated the expected term based on the expected time to a liquidity event. The risk-free interest rate was based on the yields of zero-coupon U.S. treasury securities. Volatility was estimated based upon an analysis of historical equity and asset volatilities of companies deemed comparable to Radionetics. The valuation amounts were adjusted by a discount for lack of marketability to account for the lack of liquidity an owner of the interest would experience for common stock in an early-stage company. The estimated value for the common stock of Radionetics and the Radionetics Warrant was $0.02 per share as of October 15, 2021 and December 31, 2021 and $0.20 per share as of December 31, 2022.

Investment in Radionetics

The Company applied the VIE model to its variable interests in Radionetics and concluded Radionetics is a VIE due to its insufficient equity to finance its activities without additional subordinated financial support.

The Company then evaluated whether it is the primary beneficiary of Radionetics by identifying Radionetics' key activities: (1) research and development activities, (2) financing decisions, and (3) determining the strategic direction of Radionetics. Power over research and development activities are made by unanimous vote by members of the research and development committee, in which no party has power. Power for financing decisions and setting strategic direction rests with the Radionetics' board of directors, and no party was determined to be in control since the Radionetics board of directors is comprised of 4 members for which Crinetics, 5AM and Frazier are entitled to appoint (and replace, as needed) their board designee while the fourth independent member must be mutually agreed to by all three investors. Radionetics' management is entirely separate from the Company and is determined by Radionetics' board of directors. As the Company does not control any of Radionetics' key activities, it is not the primary beneficiary of the VIE and does not consolidate Radionetics.

The Company accounted for its investment in Radionetics under the equity method of accounting due to its ability to exercise significant influence through its board seat and involvement in R&D activities, among other factors. The Company's initial investment in Radionetics was recorded at the fair value of common stock received in the amount of $1.0 million.

The Company's maximum exposure to loss of Radionetics is limited to carrying value of its equity method investment in Radionetics and the Radionetics Warrant. The Company has no obligation to fund the operations of Radionetics and has not provided significant explicit or implicit support to Radionetics that was not contractually required. The financial statements of Radionetics are not received sufficiently timely for the Company to record its portion of earnings or loss in the current consolidated financial statements and therefore the Company reports its portion of earnings or loss on a one quarter lag. The Company accounted for its share in Radionetics' loss as of December 31, 2021 during the first quarter of 2022. The Company's investment in Radionetics was written down to zero during the first quarter of 2022 as a result of the allocation of the Company's share of losses of the investee.

Other Radionetics Transactions

During the year ended December 31, 2021, Radionetics completed a $30.0 million convertible notes financing with 5AM and Frazier as the sole participants.

R. Scott Struthers, Ph.D. the Company's President and Chief Executive Officer, serves as chairman of the Radionetics board of directors. Pursuant to such arrangement, Dr. Struthers received 1,000,000 shares of restricted common stock of Radionetics, which vest ratably over 36 months, subject to his continued service, and he receives a $50,000 annual retainer for his service as a board member of Radionetics.

As of December 31, 2022 and 2021, the Company had approximately $0.1 million and $0.6 million, respectively, due from Radionetics for reimbursement of certain expenses paid on behalf of Radionetics. These amounts are recorded within prepaid expenses and other current assets in the accompanying consolidated balance sheets. During the years ended December 31, 2022 and 2021, the Company had approximately $0.4 million and $0.6 million, respectively, of reimbursements earned from Radionetics. The Company has evaluated these reimbursements and concluded that these reimbursements are not performance obligations for which the Company is acting as the principal and therefore these amounts have been included within operating expenses in the accompanying statements of operations and comprehensive loss in the period incurred.

Sanwa Kagaku Kenkyusho Co., Ltd

On February 25, 2022, the Company and Sanwa Kagaku Kenkyusho Co., Ltd. ("Sanwa"), entered into a license agreement (the "Sanwa License") whereby the Company granted Sanwa an exclusive license to develop and commercialize paltusotine in Japan.

Under the Sanwa License, Sanwa has the right to receive data obtained by the Company through certain paltusotine studies. The Company assessed the Sanwa License and concluded that Sanwa is a customer within the agreement. Sanwa will assume all costs associated with clinical trials and regulatory applications associated with these processes in Japan. Further, the Company retains all rights to develop and commercialize the product outside Japan. The Company also granted Sanwa the right to purchase supply of paltusotine for clinical and commercial requirements at cost plus a pre-negotiated percentage which was considered to be a market rate and therefore not a material right.

The Company determined that its performance obligations under the Sanwa License comprised the license and data exchange. Certain professional services, such as the Company's participation on committees, were deemed to be immaterial to the context of the contract.

In exchange, the Company received a $13.0 million nonrefundable, upfront payment and will be eligible to receive up to an additional $25.5 million in milestone payments related to the achievement of certain development, regulatory and commercial goals. In addition, upon market approval of paltusotine in Japan, the Company will be eligible to receive certain sales-based royalties. The Company determined that the transaction price amounted to the upfront payment of $13.0 million. As there have been no sales to date, no sales-based milestones or royalties were recognized to date. Further, using the most-likely-method, the developmental milestone payments were considered fully constrained.

The control of the license was transferred to Sanwa at the inception of the contract and the Company does not have an ongoing performance obligation to support or maintain the licensed intellectual property. Revenue allocated to the data exchange obligation is recognized over time using the cost-to-cost measure as this method represents a faithful depiction of progress toward the ongoing paltusotine studies in the U.S. and related data transfer. Revenue is recognized on a gross basis as the Company is the principal.

Licenses revenue for the year ended December 31, 2022 was comprised of $1.5 million at inception of the contract upon transferring the license at a point in time and $3.2 million recognized over time from the data exchange. As of December 31, 2022, $2.2 million and $6.1 million is included as current deferred revenues and non-current deferred revenues, respectively, in the accompanying consolidated balance sheets. Deferred revenues are expected to be recognized over the duration of certain paltusotine studies conducted by the Company.

On June 14, 2022, the Company and Sanwa, entered into a clinical supply agreement (the "Sanwa Clinical Supply Agreement") whereby the Company is responsible for manufacturing and supplying certain materials to Sanwa for the completion of certain studies and trials under the Sanwa License. During the year ended December 31, 2022, the Company recognized $0.1 million of revenues through the Sanwa Clinical Supply Agreement.

9. STOCKHOLDERS' EQUITY

Stock Offerings

On April 17, 2020, the Company completed a public offering of 8,222,500 shares of its common stock at a public offering price of $14.00 per share. Proceeds from the offering were approximately $107.9 million, net of underwriting discounts and commissions and offering costs of $7.3 million. The shares were registered pursuant to the Company's Shelf Registration Statement discussed below.

On April 12, 2021, the Company completed an underwritten follow-on offering of 4,562,044 shares of its common stock at a price to the public of $16.44 per share. Proceeds from the offering were approximately $72.6 million, net of underwriting discounts and commissions and offering costs of $2.4 million. The shares were registered pursuant to the Company's Shelf Registration Statement discussed below.

On July 28, 2021, the Company entered into a stock purchase agreement for the private placement of 851,306 shares of its common stock at a price of $17.62 per share (the "Private Placement"), which shares were issued on July 30, 2021. Proceeds from the offering were approximately $15.0 million.

On October 21, 2021, the Company completed an underwritten follow-on offering of 8,712,400 shares of its common stock at a price to the public of $19.80 per share. Proceeds from the offering were approximately $162.0 million, net of underwriting discounts and commissions and offering costs of $10.5 million. The shares were registered pursuant to the Company's 2021 Shelf Registration Statement discussed below.

On April 18, 2022, the Company completed an underwritten follow-on offering of 5,625,563 shares of its common stock at a price to the public of $22.22 per share. Net proceeds from the offering were approximately $117.2 million, after underwriting discounts and commissions and estimated offering costs of approximately $7.8 million. The shares were registered pursuant to the Company's 2021 Shelf Registration Statement.

Shelf Registration Statements and ATM Offering

On August 13, 2019, the Company filed a registration statement on Form S-3 (the "2019 Shelf Registration Statement"), covering the offering of up to $300.0 million of common stock, preferred stock, debt securities, warrants and units. The 2019 Shelf Registration Statement became effective on August 29, 2019.

On August 13, 2019, the Company also entered into a Sales Agreement (the "Sales Agreement") with SVB Leerink LLC and Cantor Fitzgerald & Co. (collectively, the "Sales Agents"), under which the Company may, from time to time, sell shares of its common stock through the Sales Agents (the "ATM Offering"). The 2019 Shelf Registration Statement included a prospectus covering the offering, issuance and sale of up to $75.0 million of the Company's common stock from time to time through the ATM Offering.

Pursuant to the 2019 Shelf Registration Statement, the Company has issued 275,764 shares of common stock in the ATM Offering for net proceeds of $6.4 million, after deducting commissions. The Company has not issued any additional shares of common stock in the ATM Offering since the first quarter of 2020. The 2019 Shelf Registration Statement expired on August 29, 2022.

On August 10, 2021, the Company filed a registration statement on Form S-3 (the "2021 Shelf Registration Statement"), which became immediately effective upon filing, covering the offering of common stock, preferred stock, debt securities, warrants and units and the resale of up to 851,306 shares by the accredited investor who purchased shares in the Private Placement.

On August 12, 2022, the Company filed with the SEC a prospectus supplement, dated August 12, 2022, to the 2021 Shelf Registration Statement pursuant to Rule 424(b) under the Securities Act of 1933, as amended, relating to the offer and sale of up to $150 million of shares of its common stock from time to time to or through the Sales Agents, pursuant to the Sales Agreement, in the ATM Offering. Following the expiration of the 2019 Shelf Registration Statement, the shares to be sold under the Sales Agreement may be issued and sold pursuant to the 2021 Shelf Registration Statement.

10. EQUITY INCENTIVE PLANS

2021 Employment Inducement Incentive Award Plan

The Company adopted the 2021 Employment Inducement Incentive Award Plan (the "2021 Inducement Plan") in December 2021. The Company initially reserved 1,500,000 shares of the Company's common stock for issuance pursuant to awards granted under the 2021 Inducement Plan. The terms of the 2021 Inducement Plan are substantially similar to the terms of the Company's 2018 Incentive Award Plan with the exception that awards may only be made to an employee who has not previously been an employee or member of the board of directors of the Company if the award is in connection with commencement of employment. No awards were granted under the 2021 Inducement Plan during the year ended December 31, 2021. In 2022, the Company amended the 2021 Inducement Plan to increase the number of shares of the Company's common stock available for future issuance under the 2021 Inducement Plan to 5,000,000 shares. As of December 31, 2022, 2,315,100 shares of common stock were available for future issuance under the 2021 Inducement Plan.

2018 Incentive Award Plan

The Company adopted the 2018 Incentive Award Plan (the "2018 Plan") in July 2018. Under the 2018 Plan, which expires in July 2028, the Company may grant equity-based awards to individuals who are employees, officers, directors or consultants of the Company. Options issued under the 2018 Plan will generally expire ten years from the date of grant and vest over a four-year period. As of December 31, 2022, an aggregate of 2,167,691 shares of common stock were available for issuance under the 2018 Plan.

The 2018 Plan contains a provision that allows annual increases in the number of shares available for issuance on the first day of each calendar year through January 1, 2028 in an amount equal to the lesser of: (i) 5% of the aggregate number of

shares of the Company's common stock outstanding on December 31 of the immediately preceding calendar year, or (ii) such lesser amount determined by the Company. Under this evergreen provision, on January 1, 2023, an additional 2,693,859 shares became available for future issuance under the 2018 Plan.

2015 Stock Incentive Plan

The Company adopted the 2015 Stock Incentive Plan (the "2015 Plan") in February 2015, which provided for the issuance of equity awards to the Company's employees, members of its board of directors and consultants. In general, options issued under this plan vest over four years and expire after 10 years. Subsequent to the adoption of the 2018 Plan, no additional equity awards can be made under the 2015 Plan.

Certain awards issued under the 2015 Plan allowed for exercise prior to vesting. Shares issued under such early-exercise provisions are subject to repurchase by the Company until they become fully vested. As of December 31, 2022, there were no unvested shares issued under early-exercise provisions were subject to repurchase by the Company. The consolidated balance sheet reflects an unvested stock liability of $2,000 as of December 31, 2021.

2018 Employee Stock Purchase Plan

The Company adopted the 2018 Employee Stock Purchase Plan (the "ESPP") in July 2018. The ESPP permits participants to purchase common stock through payroll deductions of up to 20% of their eligible compensation. As of December 31, 2022, an aggregate of 1,200,455 shares of common stock were available for issuance under the ESPP.

The ESPP contains a provision that allows annual increases in the number of shares available for issuance on the first day of each calendar year through January 1, 2028 in an amount equal to the lesser of: (i) 1% of the aggregate number of shares of the Company's common stock outstanding on December 31 of the immediately preceding calendar year, or (ii) such lesser amount determined by the Company. Under this evergreen provision, on January 1, 2023, an additional 538,771 shares became available for future issuance under the ESPP.

Stock Awards

Stock Options

Activity under the Company's stock option plans during the year ended December 31, 2022 was as follows:

	Options Outstanding	Weighted-Average Exercise Price	Weighted-Average Remaining Term	Aggregate Intrinsic Value (000's)
Balance at December 31, 2021	6,553,594	$ 16.07		
Granted	4,139,204	$ 19.54		
Exercised	(524,774)	$ 9.00		
Forfeited and expired	(410,695)	$ 19.28		
Balance at December 31, 2022	9,757,329	$ 17.79	8.0	$ 23,149
Vested and expected to vest at December 31, 2022	9,757,329	$ 17.79	8.0	$ 23,149
Exercisable at December 31, 2022	4,122,612	$ 15.90	6.6	$ 18,493

Aggregate intrinsic value is calculated as the difference between the closing price of the Company's common stock at December 31, 2022 and the exercise price of stock options that had strike prices below the closing price.

The total intrinsic value of options exercised during 2022, 2021 and 2020 was $5.9 million, $5.1 million and $2.5 million, respectively.

The total fair value of options vested during 2022, 2021 and 2020 was $23.0 million, $16.3 million and $9.9 million, respectively.

Restricted Stock Units

The Company's restricted stock unit activity during the year ended December 31, 2022 was as follows:

	Restricted Stock Units Outstanding	Weighted-Average Grant Date Fair Value
Balance at December 31, 2021	—	$ —
Granted	319,419	$ 19.90
Forfeited	(29,108)	$ 20.02
Balance at December 31, 2022	290,311	$ 19.88

Fair Value of Stock Awards

The Company estimate the fair value of all stock option grants and ESPP using the Black-Scholes option pricing model and recognize forfeitures as they occur.

The following table summarizes the weighted average assumptions used to estimate the fair value of stock options granted under the Company's stock option plans and the shares purchasable under the ESPP during the periods presented:

	Year ended December 31,		
Stock Option Awards	**2022**	**2021**	**2020**
Expected term	6.1 years	6.0 years	6.0 years
Expected volatility	88%	86%	78%
Risk free interest rate	2.8%	1.0%	0.8%
Expected dividend yield	—%	—%	—%

	Year ended December 31,		
ESPP	**2022**	**2021**	**2020**
Expected term	1.3 years	1.6 years	1.4 years
Expected volatility	87%	91%	84%
Risk free interest rate	4.1%	0.3%	0.2%
Expected dividend yield	—%	—%	—%

The weighted-average fair value of stock options granted to employees during the years ended December 31, 2022, 2021 and 2020 was $14.50, $13.02 and $12.83 per share, respectively. The weighted-average fair value of awards under the ESPP during the years ended December 31, 2022, 2021 and 2020 was $9.39, $12.52 and $8.07 per share, respectively.

The key assumptions used in determining the fair value of equity awards, and the Company's rationale, were as follows: (i) *Expected term* - the expected term for options represents the period that options are expected to be outstanding and has been estimated using the simplified method, which is an average of the contractual option term and its vesting period; the expected term for ESPP represents the term the awards are expected to be outstanding; (ii) *Expected volatility* - the expected volatility assumption is based on volatilities of a peer group of similar companies in the biotechnology industry whose share prices are publicly available. The Company computes the historical volatility data using the daily close prices for the selected companies' shares during the equivalent period of the calculated expected term of the Company's stock-based awards. The Company will continue to apply this process until sufficient historical information regarding the volatility of its common stock price becomes available or the Company believes the volatility of its own market-traded shares best represent expected volatility; (iii) *Risk-free interest rate* - the risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for zero coupon U.S. Treasury notes with maturities that approximate the expected terms of awards; and (iv) *Expected dividend yield* - the expected dividend yield assumption is zero as the Company has never paid dividends and has no present intention to do so in the future.

Restricted stock units are valued using the grant date stock price.

Stock-Based Compensation Expense

Stock-based compensation expense for the equity awards issued by the Company to employees and non-employees for the periods presented below was as follows (*in thousands*):

	Year ended December 31,		
	2022	**2021**	**2020**
Included in research and development	$ 15,078	$ 9,654	$ 5,218
Included in general and administrative	13,190	7,698	5,209
Total stock-based compensation expense	$ 28,268	$ 17,352	$ 10,427

As of December 31, 2022, unrecognized stock-based compensation cost related to option awards, restricted stock units, and ESPP was $72.5 million, $4.5 million and $2.8 million, respectively, which is expected to be recognized over a remaining weighted-average period of approximately 2.1 years, 3.1 years and 1.8 years, respectively.

11. INCOME TAXES

The Company is subject to taxation in the United States, various state jurisdictions and Australia; however, as it has operated at a loss since inception, it has not paid income taxes in any of the jurisdictions in which it has operated. At December 31, 2022, the Company had federal, state, and foreign net operating loss ("NOL") carryforwards of approximately $254.5

million, $218.0 million and $1.3 million, respectively. The federal loss carryforwards generated after 2017 of $248.1 million will carryforward indefinitely and can be used to offset up to 80% of future annual taxable income, while those loss carryforwards generated prior to 2018 begin expiring in 2035, unless previously utilized. $0.5 million of the state loss carryforwards will carryforward indefinitely. The other state loss carryforwards begin expiring in 2035, unless previously utilized. The Company's foreign loss carryforwards do not expire. The Company also has federal and California R&D credit carryforwards and federal Orphan Drug Credits totaling $8.8 million, $6.1 million, and $12.5 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.

The Company’s NOL and credit carryforwards to offset future taxable income may be subject to a substantial annual limitation upon future utilization as a result of ownership changes that could occur in the future pursuant to Internal Revenue Code Sections 382 and 383. These ownership changes may limit the amount of NOL and credit carryforwards that can be utilized to offset future taxable income and income tax, respectively. In general, an “ownership change” as defined by the tax code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percent of the outstanding stock of a company by certain stockholders or public groups. During 2020, the Company completed a study to assess whether an ownership change within the meaning of Section 382 had occurred for the time period prior to July 15, 2020. The study identified several such ownership changes during the study period, which resulted in limitations on the annual utilization of the Company’s NOL and credit carryforwards, or the “Tax Attribute” carryforwards; however, the study findings also indicated that none of the Company’s Tax Attribute carryforwards generated during the study period would expire solely as a result of annual limitations on the utilization of such Tax Attribute carryforwards. The Company updated the study for 2022 and did not identify any additional ownership changes. Future ownership changes could still occur which might place further limits on the Company’s ability to utilize its Tax Attribute carryforwards.

The Company’s federal income tax returns from 2019 forward, state income tax returns from 2018 forward, and its Australian tax returns beginning in 2020 are subject to examination by tax authorities; however, the Company's tax attribute carryforwards such as NOLs and R&D credits generated in closed tax years remain subject to adjustment by the taxing authorities until the future tax years in which those attributes are utilized are closed to statute. No such audits are underway.

Deferred tax assets and liabilities

Net deferred tax assets are comprised of the following as of December 31, 2022 and 2021 (*in thousands*):

	December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 69,044	$ 59,453
Capitalized research expenses	22,123	3,598
R&D and other tax credits	22,210	12,930
Stock-based compensation	8,168	5,899
Lease liability	648	1,125
Accrued expenses and other, net	4,208	3,309
Total deferred tax assets	126,401	86,314
Deferred tax liabilities:		
Right-of use asset	(313)	(531)
Equity method investment	(140)	(302)
Net of deferred tax assets and liabilities	125,948	85,481
Less: valuation allowance	(125,948)	(85,481)
Net deferred tax assets	$ —	$ —

Realization of deferred tax assets is dependent upon future earnings, if any, the timing and amount of which are uncertain. Management assesses the available positive and negative evidence to estimate if sufficient future taxable income will be generated to use existing deferred tax assets. Based on the weight of available evidence, including the Company’s history of operating losses, management has determined that it is more likely than not that the Company’s net deferred tax assets will not be realized. Accordingly, a valuation allowance has been established by the Company to fully offset these net deferred tax assets.

Income tax benefit

For the three years in the period ended December 31, 2022, domestic and foreign pre-tax loss were (*in thousands*):

	Year ended December 31,		
	2022	2021	2020
Loss before income taxes - Domestic	$ (163,175)	$ (107,723)	$ (71,769)
Income (loss) before income taxes - Foreign	(743)	82	(2,043)
Loss before income taxes - Consolidated	$ (163,918)	$ (107,641)	$ (73,812)

A reconciliation of income tax expense to the amount computed by applying the statutory federal income tax rate to the loss from operations for the three years in the period ended December 31, 2022 is as follows (*in thousands*):

	Year ended December 31,		
	2022	2021	2020
Expected income tax benefit at federal statutory rate	$ (34,423)	$ (22,605)	$ (15,417)
State income tax benefit, net of federal benefit	(128)	(7,083)	(4,886)
Tax effect of			
Change in valuation allowance	39,733	34,495	22,242
R&D credit	(10,918)	(7,117)	(2,597)
Stock-based compensation	781	1,196	539
Australian tax incentive	266	27	215
State rate change	3,243	(8)	(5)
Other	1,446	1,095	(91)
Provision for income taxes	$ —	$ —	$ —

Changes to the Company's unrecognized tax benefits are summarized in the following table (*in thousands*):

	Year ended December 31,		
	2022	2021	2020
Beginning balance	$ 1,553	$ 1,092	$ 886
Increase (decrease) for prior year tax positions	837	(34)	(163)
Increase (decrease) for current year tax positions	1,720	495	369
Ending balance	$ 4,110	$ 1,553	$ 1,092

Due to the existence of the valuation allowance, future changes in unrecognized tax benefits would not have any effect on the Company's effective tax rate. The Company does not foresee any material changes to its unrecognized tax benefits within the next twelve months. There have been no decreases in unrecognized tax benefits due to settlements or expiration of statute of limitations for the assessment of taxes during the years ended December 31, 2022, 2021 and 2020.

The Company's policy is to recognize the interest expense and/or penalties related to income tax matters as a component of income tax expense. The Company had no accrual for interest or penalties on its consolidated balance sheets as of December 31, 2022 or December 31, 2021, and has not recognized interest and/or penalties in its consolidated statements of operations for the years ended December 31, 2022 and December 31, 2021 as the unrecognized tax benefits relate to tax positions for which no cash tax liability has been reduced.

In response to the pandemic, the Coronavirus Aid, Relief and Economic Security Act (the "CARES Act") was signed into law on March 27, 2020. The CARES Act, among other things, includes tax provisions relating to refundable payroll tax credits, deferment of employer's social security payments, net operating loss utilization and carryback periods, modifications to the net interest deduction limitations and technical corrections to tax depreciation methods for qualified improvement property. The CARES Act did not have a material impact on our income tax provision for the year ended December 31, 2022, 2021, and 2020.

Deferred income taxes have not been provided for undistributed earnings of the Company's consolidated foreign subsidiary because the Parent entity would not be required to include the distribution into income as the amount would be tax free.

The Tax Cuts and Jobs Act subjects a U.S. shareholder to tax on Global Intangible Low-Taxed Income ("GILTI") earned by certain foreign subsidiaries. The FASB Staff Q&A, Topic 740 No. 5. *Accounting for Global Intangible Low-Taxed Income*, states that an entity can make an accounting policy election to either recognize deferred taxes for temporary basis differences

expected to reverse as GILTI in future years or to provide for the tax expense related to GILTI in the year the tax is incurred as a period expense only. We have elected to account for GILTI in the year the tax is incurred.

12. EMPLOYEE SAVINGS PLAN

The Company has a defined contribution 401(k) benefit plan (the "401(k) Plan") for all eligible employees, effective May 1, 2016. The plan permits participants to contribute up to the amount allowable under federal limits of annual pre-tax compensation to the 401(k) Plan. Effective in 2021, discretionary matching contributions to the 401(k) Plan are permitted in an amount equal to 50% of the first 6% of the employee's taxable income up to a maximum of $3,000 per year. The Company accrued approximately $0.5 and $0.3 million for matching contributions for the years ended December 31, 2022 and 2021, respectively.

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
3.1	Amended and Restated Certificate of Incorporation	8-K	7/20/2018	3.1	
3.2	Amended and Restated Bylaws	8-K	4/14/2020	3.1	
4.1	Specimen Stock Certificate Evidencing the Shares of Common Stock	S-1/A	7/09/2018	4.1	
4.2	Amended and Restated Investor Rights Agreement, dated February 9, 2018, by and among the Registrant and certain of its stockholders	S-1	6/22/2018	4.2	
4.3	Description of Registered Securities	10-K	3/30/2021	4.3	
10.1#	Crinetics Pharmaceuticals, Inc. 2015 Stock Incentive Plan, as amended	S-1/A	7/09/2018	10.1	
10.2#	Form of stock option agreement under Crinetics Pharmaceuticals, Inc. 2015 Stock Incentive Plan, as amended	S-1	6/22/2018	10.2	
10.3#	Crinetics Pharmaceuticals, Inc. 2018 Incentive Award Plan	S-1/A	7/09/2018	10.3	
10.4#	Form of stock option agreement under Crinetics Pharmaceuticals, Inc. 2018 Incentive Award Plan	S-1/A	7/09/2018	10.4	
10.5#	Form of restricted stock unit agreement under Crinetics Pharmaceuticals, Inc. 2018 Incentive Award Plan	10-K	3/30/2022	10.5	
10.6#	Crinetics Pharmaceuticals, Inc. 2018 Employee Stock Purchase Plan and offering document thereunder	S-1/A	7/09/2018	10.5	
10.7#	Amended and Restated Employment Agreement, effective as of May 25, 2018, by and between R. Scott Struthers and the Registrant	S-1	6/22/2018	10.6	
10.8#	Amended and Restated Employment Agreement, effective as of May 22, 2018, by and between Marc J.S. Wilson and the Registrant	S-1	6/22/2018	10.7	
10.9#	Employment Agreement, effective as of June 15, 2018, by and between Alan Krasner, M.D. and the Registrant	S-1/A	7/09/2018	10.8	
10.10#	Amended and Restated Employment Agreement, effective as of May 22, 2018, by and between Ajay Madan and the Registrant	10-Q	8/07/2020	10.1	
10.11#	Form of Indemnification Agreement for Directors and Officers	S-1/A	7/09/2018	10.9	
10.12	Lease Agreement, dated as of February 21, 2018, by and between 6262 Lusk Investors LLC and the Registrant, as amended	S-1	6/22/2018	10.9	
10.13†	Lease Agreement, dated as of September 9, 2022, by and between San Diego 1 LLC and the Registrant	10-Q	11/14/2022	10.1	
10.14#	Amended and Restated Non-Employee Director Compensation Program	10-Q	5/06/2021	10.1	
10.15	Sales Agreement, dated August 13, 2019, among the Company, SVB Leerink LLC and Cantor Fitzgerald & Co.	S-3	8/13/2019	1.2	
10.16#	Stock Purchase Agreement, dated July 28, 2021, by and among the Company and the Purchaser named therein	8-K	7/29/2021	99.1	
10.17#	Crinetics Pharmaceuticals, Inc. 2021 Employment Inducement Incentive Award Plan and Form of Stock Option Agreement thereunder	8-K	12/23/2021	10.1	
10.18#	Amendment to the Crinetics Pharmaceuticals, Inc. 2021 Employment Inducement Incentive Award Plan	10-Q	11/14/2022	10.3	

10.19#	Amendment No. 2 to the Crinetics Pharmaceuticals, Inc. 2021 Employment Inducement Incentive Award Plan				X
10.20#	Form of restricted stock unit agreement under Crinetics Pharmaceuticals, Inc. 2021 Employment Inducement Incentive Award Plan	10-K	3/30/2022	10.17	
10.21#	Amended and Restated Employment Agreement, effective as of May 22, 2018, by and between Stephen Betz and the Registrant	10-K	3/30/2022	10.18	
10.22#	Employment Agreement, effective as of September 13, 2021, by and between Jeff Knight and the Registrant	10-K	3/30/2022	10.19	
10.23#	Employment Agreement, effective as of February 16, 2022, by and between James Hassard and the Registrant	10-K	3/30/2022	10.20	
10.24#	Employment Agreement, effective as of September 30, 2022, by and between Dana Pizzuti and the Registrant	10-Q	11/14/2022	10.2	
10.25#	Consulting Agreement, dated as of April 1, 2022, by and between Ajay Madan and the Registrant	10-Q	5/12/2022	10.3	
10.26†	License Agreement, dated as of February 25, 2022, by and between Sanwa Kagaku Kenkyusho Co., Ltd. and the Registrant	10-Q	5/12/2022	10.2	
21.1	List of Subsidiaries of the Registrant	S-1	6/22/2018	21.1	
23.1	Consent of BDO USA, LLP, independent registered public accounting firm				X
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				X
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				X
101.INS	INLINE XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags				X
101.SCH	INLINE XBRL Taxonomy Extension Schema Document				X
101.CAL	INLINE XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	INLINE XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	INLINE XBRL Taxonomy Extension Label Linkbase Document				X
101.PRE	INLINE XBRL Taxonomy Extension Presentation Linkbase Document				X
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)				X

† Portions of this exhibit have been omitted in compliance with Regulation S-K Item 601(b)(10)(iv).
# Indicates management contract or compensatory plan.
* These certifications are being furnished solely to accompany this annual report pursuant to 18 U.S.C. Section 1350 and are not being filed for purposes of Section 18 of the Securities Exchange Act of 1934 and are not to be incorporated by reference

into any filing of the Registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

Crinetics Pharmaceuticals, Inc.

Date: February 28, 2023

By: /s/ R. Scott Struthers, Ph.D.
R. Scott Struthers, Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ R. Scott Struthers, Ph.D. **R. Scott Struthers, Ph.D.**	President, Chief Executive Officer and Director (principal executive officer)	February 28, 2023
/s/ Marc J.S. Wilson **Marc J.S. Wilson**	Chief Financial Officer (principal financial and accounting officer)	February 28, 2023
/s/ Wendell Wierenga, Ph.D. **Wendell Wierenga, Ph.D.**	Chairman of the Board of Directors	February 28, 2023
/s/ Camille Bedrosian, M.D. **Camille Bedrosian, M.D.**	Director	February 28, 2023
/s/ Caren Deardorf **Caren Deardorf**	Director	February 28, 2023
/s/ Matthew K. Fust **Matthew K. Fust**	Director	February 28, 2023
/s/ Weston Nichols, Ph.D. **Weston Nichols, Ph.D.**	Director	February 28, 2023
/s/ Stephanie Okey **Stephanie Okey**	Director	February 28, 2023
/s/ Rogério Vivaldi Coelho, M.D. **Rogério Vivaldi Coelho, M.D.**	Director	February 28, 2023

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