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, 2019

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	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001 per share	**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 is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

As of June 28, 2019 (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 $422.8 million, based on the closing price of the registrant's common stock on the Nasdaq Global Select Market on such date of $25.00 per share.

The number of outstanding shares of the registrant's common stock, par value 0.001 per share, as of February 28, 2020 was 24,566,896.

DOCUMENTS INCORPORATED BY REFERENCE

Certain sections of the registrant's definitive proxy statement for the 2020 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, 2019

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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 will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

Item 1. Business

Business 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 assembled a seasoned team with extensive expertise in drug discovery and development in endocrine GPCRs and built a highly productive drug discovery organization. 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 lead product candidate, paltusotine (formerly CRN00808), is currently in clinical development for the treatment of acromegaly, and we are advancing additional product candidates through clinical and preclinical 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 clinical and preclinical programs:

- Paltusotine, our lead product candidate, establishes a new class of oral selective nonpeptide somatostatin receptor type 2, or sst2, biased 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. More than 25,000 people in the United States suffer from acromegaly, and an estimated 40% to 60% 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 171,000 adults in the United States. 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 guidelines. In 2019, injected

somatostatin peptide drugs accounted for approximately $3.1 billion in global sales for the treatment of acromegaly, NETs and other uses. Currently marketed peptide 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.

In March 2018, we reported initial results from a Phase 1, double-blind, randomized, placebo-controlled, single- and multiple-ascending dose trial to evaluate the safety, pharmacokinetics, or PK, and pharmacodynamics, or PD, of paltusotine in 99 healthy volunteers. Paltusotine demonstrated clinical proof-of-concept by potently suppressing stimulated GH and baseline IGF-1 in these subjects. The plasma exposure of paltusotine indicated the drug was well absorbed with a half-life of 42 to 50 hours, supporting once daily administration in patients. The safety and tolerability of paltusotine observed in this trial was generally consistent with that of approved peptide somatostatin analogs, or SSAs.

We are currently conducting three global Phase 2 clinical trials of paltusotine in acromegaly patients, the ACROBAT EVOLVE, or EVOLVE, ACROBAT EDGE, or EDGE, and ACROBAT ADVANCE, or ADVANCE trials. The EVOLVE trial is a double-blind, placebo-controlled, randomized withdrawal study designed to evaluate the safety, efficacy and pharmacokinetics of paltusotine, in subjects with acromegaly whose disease is biochemically controlled by octreotide LAR or lanreotide depot monotherapy. The EDGE trial is an open label exploratory study designed to evaluate the safety, efficacy and pharmacokinetics of paltusotine in subjects with acromegaly that are treated with somatostatin analog based treatment regimens but whose disease is not biochemically controlled by monotherapy. The ADVANCE trial is an open label, long term extension study designed to evaluate the safety and efficacy of paltusotine in patients that have completed the EVOLVE or EDGE trials. We dosed the first patients in the EVOLVE and EDGE trials in March 2019.

- CRN01941 is also an oral nonpeptide sst2 biased agonist initially in development for the treatment of NETs. We initiated a Phase 1 clinical trial in May 2019 to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of CRN01941 and expect results from this trial in early 2020. We intend to decide whether to advance CRN01941 or paltusotine into a later stage trial in NETs upon analysis of the cumulative data from the paltusotine and CRN01941 preclinical, nonclinical and clinical programs.
- We are developing the first nonpeptide product candidate to antagonize peptide adrenocorticotrophic hormone, or ACTH, designed for the treatment of Cushing's disease and other diseases caused by excess ACTH, including congenital adrenal hyperplasia, or CAH and Ectopic ACTH Syndrome, or EAS. 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. Cushing's disease is an orphan indication with a prevalence of approximately 12,000 patients in the United States. We are currently conducting first-in-human enabling studies with our lead ACTH antagonist development candidate.
- We are developing a new class of oral selective nonpeptide somatostatin type 5 receptor, or sst5, agonists designed to treat congenital hyperinsulinism, or CHI. This is a devastating rare disease in which infants are born with mutations that cause excess secretion of the pancreatic hormone insulin resulting in profound hypoglycemia, a very low level of blood glucose. This loss of homeostatic control of blood glucose levels can lead to seizures, developmental disorders, learning disabilities, coma and even death. CHI occurs in approximately 1 in 30,000 to 50,000 new births in the United States. We are currently conducting first-in-human enabling studies with our lead sst5 agonist development candidate.

Patients with many other debilitating endocrine diseases await new therapeutic options, and we are continuously evaluating where next to deploy our drug discovery efforts. All of our product candidates have been discovered, characterized and developed internally and are the subject of composition of matter patent applications, including issued U.S. patents covering paltusotine extending to 2037. We have retained worldwide rights to commercialize our product candidates and do not have any royalty obligations. Over time, we intend to sell our products, if approved, through our own commercial organization, which we believe can be of modest size to cover the relatively small number of specialty endocrinologists who treat patients with rare endocrine diseases and endocrine-related tumors.

We were founded by a team of scientists with a track record of drug discovery and development to create important new therapeutic options for patients with rare endocrine diseases. Prior to founding the company, our Chief Executive Officer, Scott Struthers, Ph.D., was Senior Director and Head of Endocrinology and Metabolism at Neurocrine Biosciences, Inc. There, Dr. Struthers and his fellow co-founders, Stephen Betz, Ph.D. and Frank Zhu, Ph.D., as well as our VP of Development Ajay Madan, Ph.D., D.A.B.T., held key leadership roles in the discovery and development of ORILISSA (elagolix), a nonpeptide product candidate designed for the treatment of endometriosis and uterine fibroids that received marketing approval from the FDA in July 2018. In addition, Dr. Madan held a key leadership role in the discovery and development of INGREZZA (valbenazine), which was approved by the FDA in 2017 for tardive dyskinesia. Our Chief Medical Officer, Alan Krasner, served as the Global Development Lead at Shire Pharmaceuticals for Natpara, the first recombinant human intact parathyroid hormone treatment for hypoparathyroidism.

Our strategy

Our objective is to transform the treatment of rare 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 rare endocrine diseases and endocrine-related tumors with significant unmet medical need.*** There are numerous rare 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 rare 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 rare 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 rare 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 commercialization rights to maximize the value of our product candidates.*** We plan to establish our own commercial organization in major markets and develop a network of third-party distributors in other selected markets. We believe this organization can be focused and modest in size due to the relatively small number of specialty endocrinologists who treat patients suffering from the diseases we target. Therefore, we do not expect that we will require larger pharmaceutical partners for commercialization of our product candidates, although we may consider partnering for certain territories or indications, or for other strategic purposes.
- ***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 biology, chemistry, 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-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.

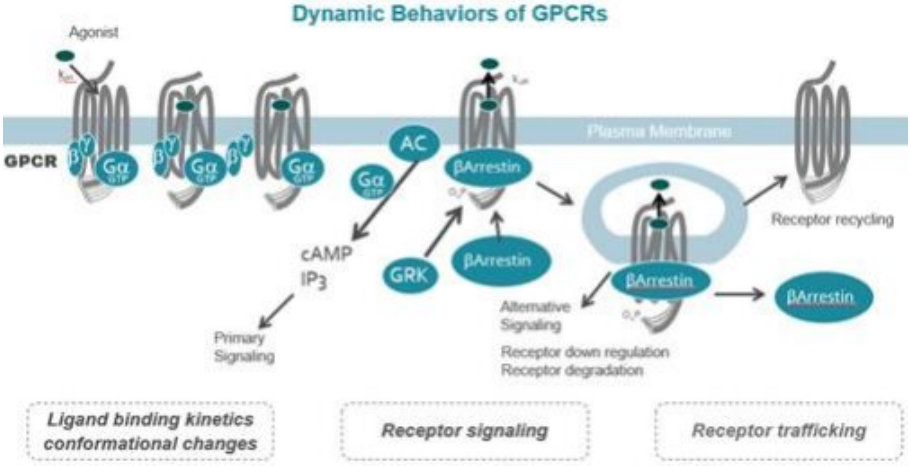


Figure 1. GPCR signaling is determined by many factors, including the binding characteristics of ligands, which dictate the responses of different signaling and regulatory pathways. Selectively favoring one pathway over others is termed biased signaling. Upon activation, GPCRs can also be trafficked into the cell, where they are either targeted for degradation or recycled back to the cell surface.

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 and anticipated milestones.

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

Our lead product, paltusotine, is an oral selective nonpeptide sst2 biased agonist in clinical development for the treatment of acromegaly. Paltusotine is the first nonpeptide sst2 agonist with reported results from a clinical trial. Initial results from our Phase 1 trial of paltusotine demonstrated clinical proof-of-concept based on observed suppression of GH and IGF-1 secretion in healthy volunteers. We submitted an Investigational New Drug application, or IND, to the FDA in August 2018 and are conducting three global Phase 2 clinical trials of paltusotine, EVOLVE, EDGE and ADVANCE in acromegaly patients. We dosed the first patients in the EVOLVE and EDGE trials in March 2019.

We have developed a second sst2 agonist, CRN01941, which, like paltusotine, is an oral, selective nonpeptide sst2 biased agonist. Both paltusotine and CRN01941 are designed for the treatment of NETs that originate from neuroendocrine cells commonly found in the gut, lung or pancreas. We are currently conducting a Phase 1 human proof-of-concept clinical trial with CRN01941 and expect results from this trial in early 2020. We intend to decide whether to advance CRN01941 or paltusotine into a later stage trial in NETs in early 2020 upon analysis of the cumulative data from the paltusotine and CRN01941 preclinical, nonclinical and clinical programs.

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. There are an estimated 25,000 patients in the United States with acromegaly.

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, an estimated 40% to 60% of 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 bromocriptine and 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.

Currently available therapies for acromegaly are 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 will often progress to liver failure. In approximately 10% of cases, these tumors are

associated with excess secretion of serotonin resulting in carcinoid syndrome, which is characterized by severe diarrhea and flushing. Patients with well- and moderately- differentiated tumors and distant metastases have a five-year survival probability of 35%, according to a study published in the Journal of Clinical Oncology. NETs are present in approximately 171,000 adults in the United States and while still an orphan disease, it is 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 of short-acting analogs as an add-on therapy. In 2017, the serotonin synthesis inhibitor, telotristat, was approved as an add-on therapy to somatostatin analogs to help prevent breakthrough symptoms of carcinoid syndrome. Second-line targeted therapies everolimus and sunitinib malate are typically only used in patients with high grade tumors which constitute only a small fraction of NETs.

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.

Paltusotine overview and clinical development

Paltusotine, our lead product candidate, pioneers a new class of oral selective nonpeptide sst2 biased 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.

Internalization and desensitization of sst2 is thought to contribute to the inability of some patients to fully respond to octreotide. Therefore, in creating paltusotine, we focused our discovery efforts on identifying biased agonists that were selective for inhibition of cAMP accumulation while minimizing receptor internalization. In vitro studies have shown that paltusotine was 75 times more potent for cAMP inhibition than receptor internalization. Figure 2 illustrates the difference in bias between octreotide and paltusotine. Concentrations of octreotide where cAMP is maximally suppressed also induced extensive internalization of sst2 receptors whereas in the same experiment, nearly all receptors remained on the cell surface at concentrations where paltusotine maximally suppressed cAMP. We believe that this increased bias suggests a reduced likelihood of desensitization of the sst2 receptor by paltusotine at pharmacologically relevant concentrations.

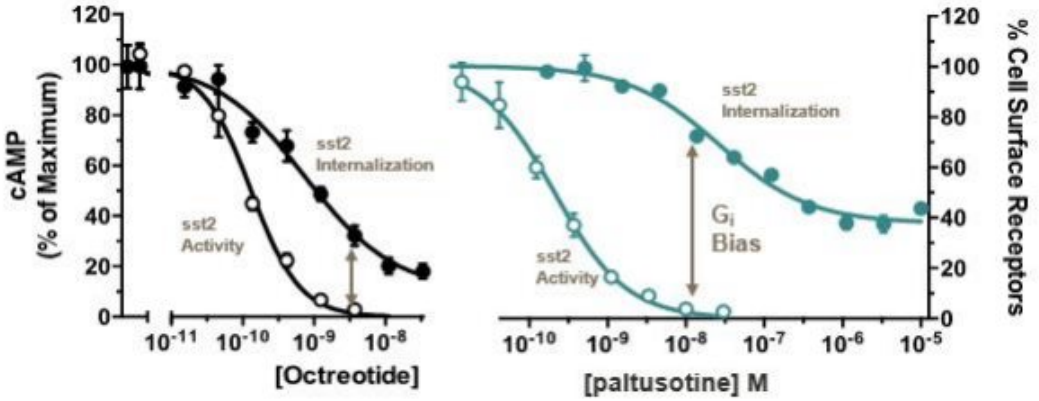


Figure 2. Dose response curves are shown from individual representative experiments. All points are the mean ± standard error of either triplicate or quadruplicate readings. White circles are from a cAMP assay measuring sst2 activation. Black circles are from an internalization assay measuring the amount of cell surface receptors. M = molar concentration.

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, and the overall trial design is shown in Figure 3. Safety, tolerability and PK were monitored in all subjects. 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. A summary of the trial cohorts and an analysis of the data from this trial is presented below.

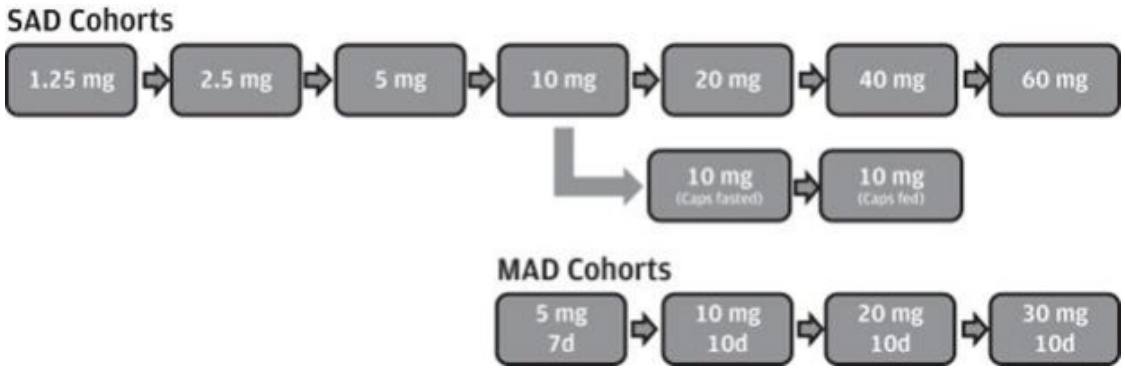


Figure 3. Design of paltusotine Phase 1 trial. The SAD phase (N=8* per cohort (6 active, 2 placebo)) initially used an oral solution (1.25-20 mg) and switched to capsules for later cohorts (40-60 mg). The 10 mg SAD cohort also compared the plasma exposure of paltusotine when it was administered as an oral solution, first generation capsules when fasted and as first-generation capsules when taken with a high-fat breakfast. The MAD phase (N=9 per cohort (6 active, 3 placebo)) only used capsules (5-30 mg). There was an additional cohort (N=8) to assess the potential for drug-drug-interactions (midazolam +/- 20 mg paltusotine). *The 20 mg SAD Cohort only enrolled 7 subjects due to a subject's last-minute cancellation.

Figure 4 shows a summary of PK-PD data from the SAD arm of the trial. As illustrated for the 10 mg cohort in Figure 4a, 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 as shown in Figure 4b. The first-generation 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 (Figure 4c). However, when the capsule was administered with a standardized high fat meal, plasma AUC was reduced by approximately 83%, suggesting that the current 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.

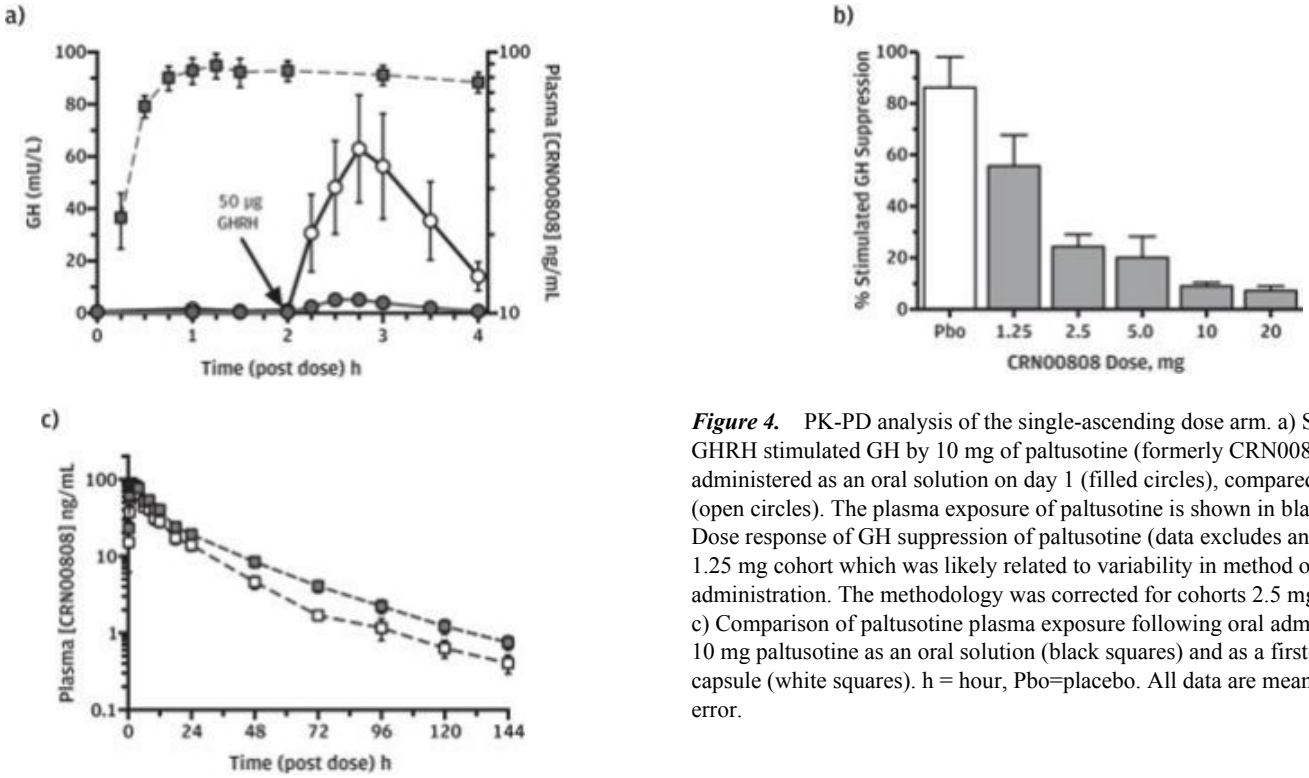


Figure 4. PK-PD analysis of the single-ascending dose arm. a) Suppression of GHRH stimulated GH by 10 mg of paltusotine (formerly CRN00808) administered as an oral solution on day 1 (filled circles), compared to day -1 (open circles). The plasma exposure of paltusotine is shown in black squares. b) Dose response of GH suppression of paltusotine (data excludes an outlier in the 1.25 mg cohort which was likely related to variability in method of GHRH administration. The methodology was corrected for cohorts 2.5 mg and higher). c) Comparison of paltusotine plasma exposure following oral administration of 10 mg paltusotine as an oral solution (black squares) and as a first-generation capsule (white squares). h = hour, Pbo=placebo. All data are mean ± standard error.

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. Figure 5a illustrates the PK-PD relationship between trough plasma paltusotine concentrations and IGF-1 levels. 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.

As shown in Figure 5b, paltusotine exhibited dose-proportional increase in exposure and a 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 (Figure 5c) 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.

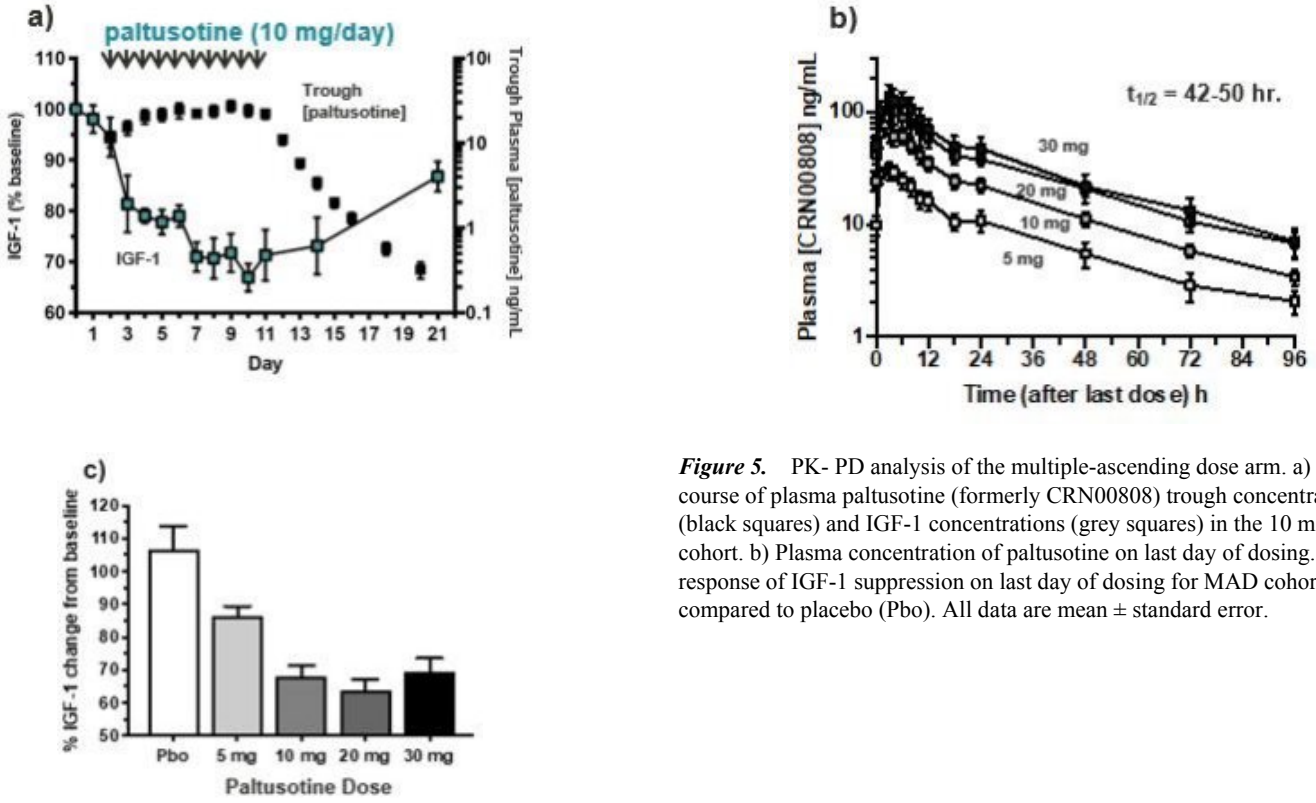


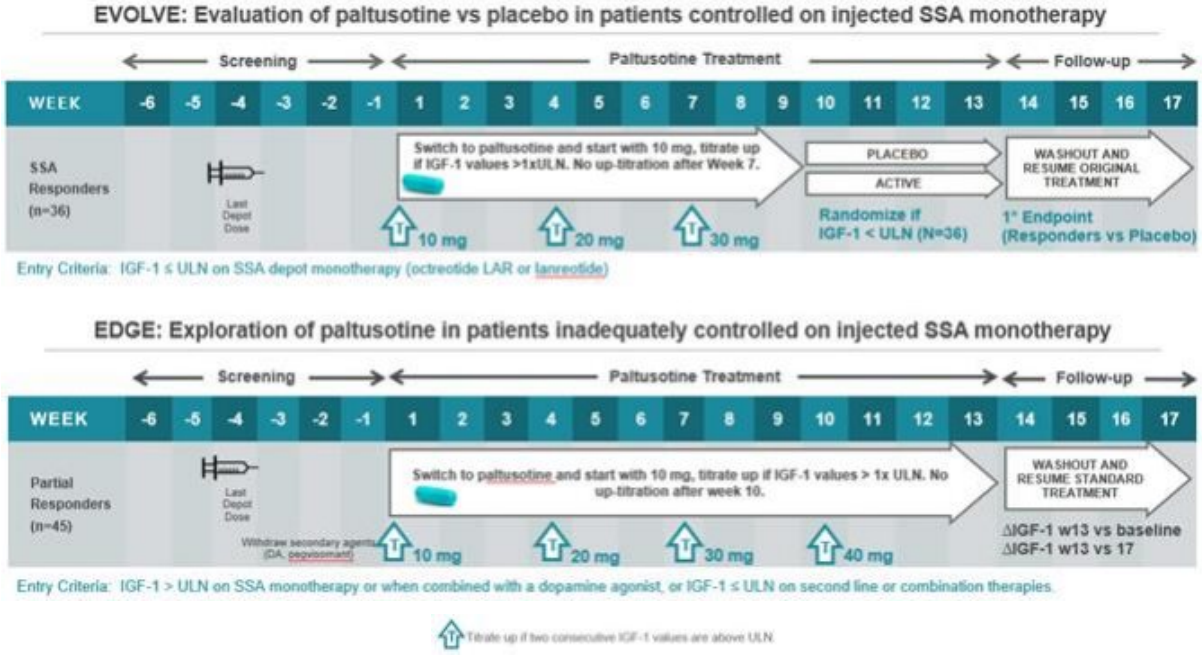
Figure 5. PK- PD analysis of the multiple-ascending dose arm. a) Time-course of plasma paltusotine (formerly CRN00808) trough concentrations (black squares) and IGF-1 concentrations (grey squares) in the 10 mg MAD cohort. b) Plasma concentration of paltusotine on last day of dosing. c) Dose response of IGF-1 suppression on last day of dosing for MAD cohorts compared to placebo (Pbo). All data are mean ± standard error.

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 in our Phase 2 trials.

Based on the initial results of our Phase 1 clinical trial, we believe we have demonstrated proof-of-concept for the ability of paltusotine to suppress the GH axis in humans. We submitted an IND application to the FDA in August 2018 and are conducting three global Phase 2 clinical trials with paltusotine in acromegaly patients. The first of these, EVOLVE, is a double-blind, randomized, placebo-controlled trial conducted in approximately 36 patients whose IGF-1 levels are biochemically controlled by octreotide or lanreotide monotherapy. We are also conducting a second, open-label exploratory trial, EDGE, to evaluate the effects of paltusotine on approximately 45 patients whose IGF-1 levels are not biochemically controlled by octreotide or lanreotide alone. We dosed the first patients in the EVOLVE and EDGE trials in March 2019. The EVOLVE and EDGE trials are being conducted globally at the same centers. 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 that have completed the EVOLVE or EDGE trials. In parallel, we are developing a second-generation formulation that may mitigate the food effect observed with the first-generation capsule.

A summary of the trial design for the EVOLVE and EDGE studies is presented below.



CRN01941 overview and preclinical development

CRN01941 is an optimized, selective, orally available, nonpeptide biased agonist of sst2 receptor initially in development for the treatment of NETs. The chemical structure of CRN01941 is derived from a different chemical scaffold from that of paltusotine. In vitro pharmacology studies demonstrated that CRN01941 potently (EC_{50}=0.1 nM) stimulated sst2 receptor activity (as measured by a decrease in cAMP accumulation in cells expressing the human sst2 receptor) and is highly biased for G_i signaling versus receptor internalization (88-fold). Analogous experiments using the other sst receptor subtypes showed selectivity for sst2 was greater than 100-fold over the other sst receptor subtypes.

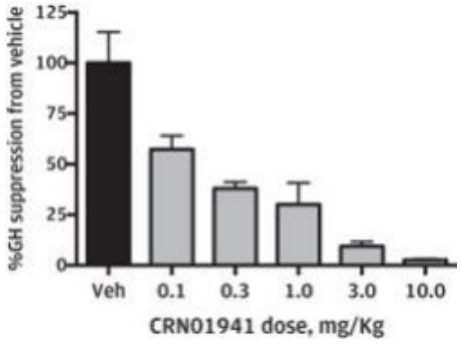


Figure 6. Suppression of GHRH-stimulated GH secretion in normal rats by CRN01941 administered as an oral solution (grey bars) compared to vehicle (black bar).

In a preclinical rodent model of efficacy, CRN01941 potently inhibited GHRH-induced GH production (Figure 6). This model is analogous to the PK-PD component in the Phase 1 clinical trial that we performed for paltusotine. In addition, the drug-like characteristics of CRN01941 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 in multiple species, synthetic accessibility and preliminary non-GLP safety assessments including 14-day screening toxicology in rats and cardiovascular safety studies in dogs.

We are currently conducting a Phase 1 human proof-of-concept clinical trial with CRN01941 and results are expected in early 2020. We intend to decide whether to advance CRN01941 or paltusotine into a later stage trial in NETs upon analysis of the cumulative data from the paltusotine and CRN01941 preclinical, nonclinical and clinical programs.

ACTH antagonists for the treatment of Cushing's disease and other diseases of ACTH excess

We have identified selective, orally available nonpeptide ACTH antagonist leads intended for the treatment of Cushing's disease that are designed to prevent excessive stimulation of the adrenal glands by the high circulating levels of ACTH found in Cushing's disease patients. We believe these drug candidates may also be developed for other diseases of ACTH excess, including CAH, a disease caused by genetic defects that prevent the production of cortisol by the adrenal gland, and EAS, a disease in which a non-pituitary tumor secretes excessive amounts of ACTH. We are currently conducting first-in-human enabling studies with our lead ACTH antagonist development candidate.

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 (collarbone, back of neck, face, trunk), 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 (known as Cushing's disease) is the most common form accounting for 60-80% of all cases and is most often due to tumors of pituitary corticotroph cells that secrete excess ACTH.

Cushing's disease is an orphan indication with a prevalence of approximately 12,000 patients in the United States. It presents much 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 occurs in 1 in 13,000 to 1 in 15,000 live births.

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.

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 recently approved 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.

The current treatment algorithm for CAH consists of lifelong daily glucocorticoid supplementation in an attempt to balance the inability to synthesize cortisol and alleviate the lack of negative feedback. 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 less 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.

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.

Product candidate discovery program

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. Our discovery team has identified potent, selective nonpeptide antagonists of MC2R designed to block ACTH action and prevent its excessive stimulation of the adrenal gland in Cushing's disease and CAH patients. In vitro and in vivo pharmacology data from one of our initial antagonists are shown in Figure 7 below. Pharmacological mechanism is confirmed both by blocking of radiolabeled ACTH in a binding assay, as well as inhibiting the agonistic ability of ACTH to stimulate cAMP in cells expressing MC2R. In vivo proof-of-concept is demonstrated by the antagonist's capacity to block corticosterone (CORT, the rat analog of cortisol) secretion in a rodent ACTH-challenge model, which mimics aspects of Cushing's disease.

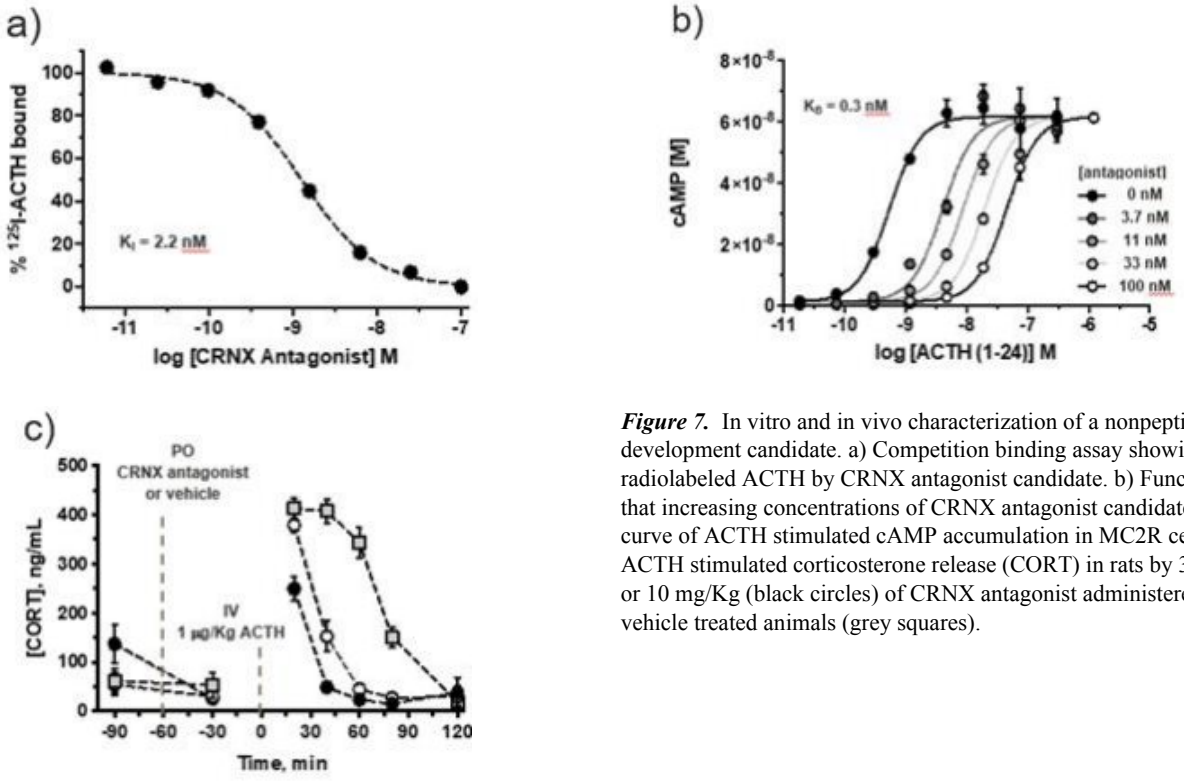


Figure 7. In vitro and in vivo characterization of a nonpeptide ACTH antagonist development candidate. a) Competition binding assay showing displacement of radiolabeled ACTH by CRNX antagonist candidate. b) Functional assay showing that increasing concentrations of CRNX antagonist candidate shift the dose-response curve of ACTH stimulated cAMP accumulation in MC2R cells. c) Suppression of ACTH stimulated corticosterone release (CORT) in rats by 3 mg/Kg (white circles) or 10 mg/Kg (black circles) of CRNX antagonist administered orally, compared to vehicle treated animals (grey squares).

We are currently conducting first-in-human enabling studies with our lead ACTH antagonist development candidate and, if successful, plan to initiate a Phase 1 human proof-of-concept clinical trial.

Somatostatin receptor type 5 agonists for the treatment of hyperinsulinemias

We have identified oral selective nonpeptide sst5 receptor agonists that are designed to inhibit the excess insulin secretion associated with congenital and acquired disorders of hyperinsulinism, with our initial focus on CHI. We are currently conducting first-in-human enabling studies with our lead sst5 agonist development candidate.

Hyperinsulinemia background

Hyperinsulinemia 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 hyperinsulinemia arises from CHI, a disorder whose underlying pathology is driven by genetic mutations in key genes involved in regulating insulin secretion from ß-cells. The incidence of CHI is approximately 1 in 30,000 to 50,000 new births in the United States. Hyperinsulinemia 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 apneas, seizures, developmental delays, learning disabilities, epilepsy and even death. Hyperinsulinemia 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. In addition, hyperinsulinemic hyperglycemia following meals in patients who have undergone gastric bypass surgery (commonly referred to as Dumping Syndrome) occurs in approximately 10 to 15% of these patients. The number of gastric bypass surgeries continues to increase, from an estimated 158,000 surgeries in 2011 to 216,000 in 2016.

Current treatments and limitations

Maintaining glucose levels through feeding or glucose infusions is the first step in managing CHI. Diazoxide is the only approved therapy indicated for hyperinsulinemia. It acts at the ATP-sensitive potassium channels, or K_{ATP}, that are involved in insulin secretion and inhibits insulin secretion. However, mutations in these channels are present in approximately 55% to 60% of CHI 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. Octreotide (used off-label) is administered as subcutaneous injections up to six times/day in those who respond poorly to diazoxide. Octreotide is an sst2 agonist, which can suppress both insulin and glucagon secretion (Figure 8). As glucagon is a primary physiologic defense mechanism against hypoglycemia, targeting sst2 is not optimal for CHI patients, and octreotide therapy fails for approximately 70% to 75% of patients. 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. 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, the surgical removal of all or a part of the pancreas.

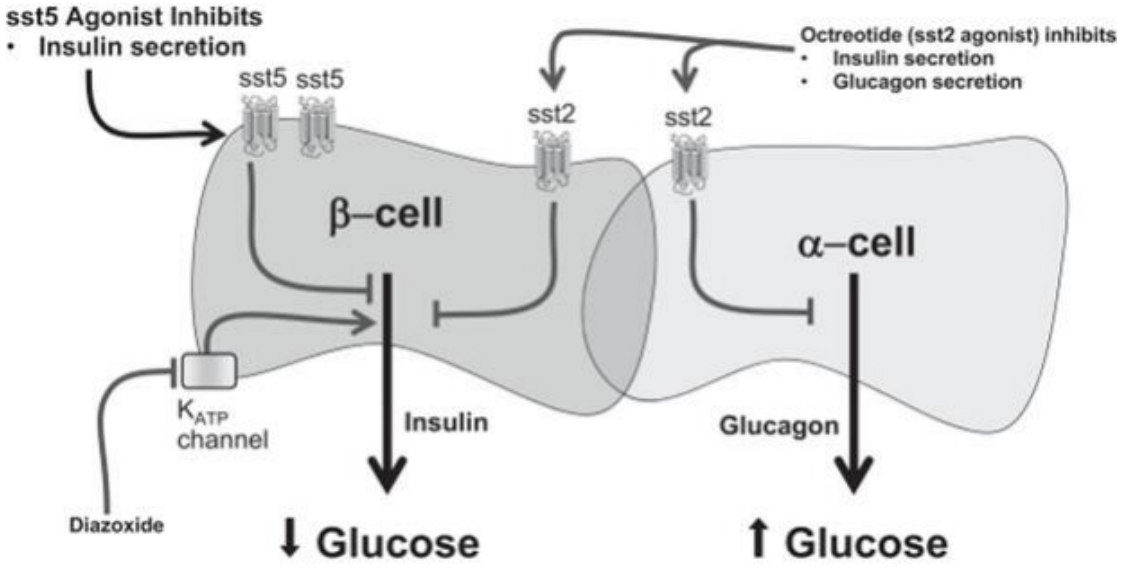


Figure 8. Hyperinsulinemia arising in CHI and the potential utility of sst5 agonists.

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.

Our lead sst5 agonist development candidate was examined in a rat model of CHI (Figure 9). In this model, rats were treated with sulfonylurea glyburide, which promotes insulin release by acting at K_{ATP} channels. This activity mimics the K_{ATP} channel mutations found in about half of CHI 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.

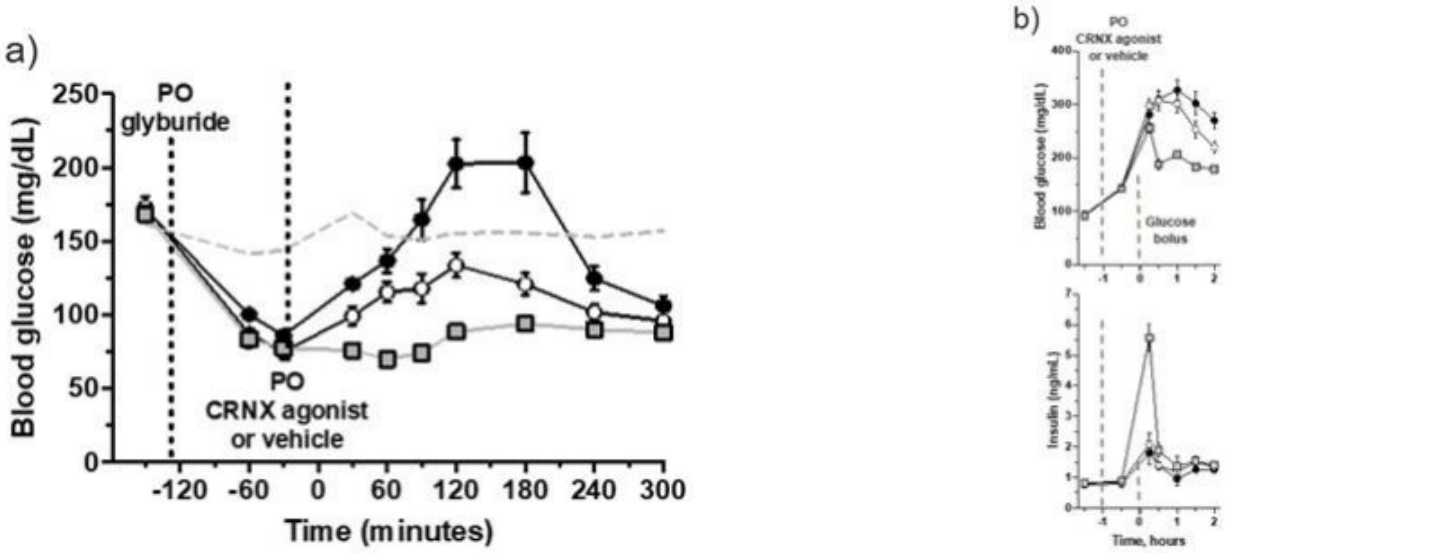


Figure 9. a) Rescue of glyburide-induced hypoglycemia by lead sst5 agonist development candidate in rats. To mimic a hypoglycemic state similar to CHI, rats were treated with the sulfonylurea glyburide (30 mg/kg, grey squares) or vehicle (dashed line). Our lead sst5 agonist development candidate was administered orally two hours after glyburide administration at either 10 mg/Kg (white circles) or 30 mg/Kg (black circles). b) Effects on glucose and insulin secretion after repeat dosing by lead sst5 agonist development candidate in rats. Vehicle (grey squares) or our lead sst5 agonist development candidate was administered once daily at either 10 mg/Kg (white circles) or 30 mg/Kg (black circles), or for 7 days. To ensure a hyperinsulinemic state on day 7, rats were administered an oral glucose bolus (1.5 mg/Kg, grey squares) one hour after compound/vehicle administration and glucose and insulin were subsequently measured. All data are mean ± standard error.

In addition, the drug-like characteristics of our lead sst5 agonist development candidate 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 in multiple species, synthetic accessibility and preliminary non-GLP safety assessments including 14-day screening toxicology in rats and cardiovascular safety studies in dogs.

Our lead sst5 agonist development candidate entered preclinical development in 2019. We are currently conducting first-in-human enabling studies with our lead sst5 agonist development candidate and, if successful, plan to initiate a Phase 1 human proof-of-concept clinical trial.

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 Novartis). 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 terms of other products in clinical development, all of them are new formulations of peptide somatostatin agonists or GH receptor antagonists. Chiasma, Inc. has submitted a New Drug Application, or NDA, to the U.S. Food and Drug Administration, or FDA, for an oral octreotide product candidate for the maintenance therapy of adult patients with acromegaly in whom prior treatment with somatostatin analogs has been shown to be effective and tolerated. Other companies developing new pharmaceutical therapies for acromegaly include Camurus AB, Dauntless Pharmaceuticals, Inc., Enesi Pharma Limited, Ionis Pharmaceuticals, Inc./Antisense Therapeutics Ltd., MidaTech Pharma PLC, Aquestive Therapeutics, Inc., 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 Lexicon Pharmaceuticals, Inc.) is an orally administered add-on therapy. Targeted therapies everolimus (marketed by Novartis) and sunitinib malate (marketed by Pfizer) are typically only used in patients with high grade tumors which constitute only a small fraction of NETs. In 2018, the FDA approved Novartis' Lutathera for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors. Companies in Phase 3 development include Progenics Pharmaceuticals, Inc. and EUSA Pharma Inc. Other companies developing products for potential use in NETs include Apeiron Scientific, LLC, Camurus, Celgene Corporation, EpicentRx, Inc., Ipsen, Mateon Therapeutics, Inc., Merck & Co., Inc., MidaTech, Novartis, Oncoceutics, Inc. and Roche Holding AG.

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. The somatostatin agonist pasireotide is also approved for Cushing's disease. Novartis and Strongbridge Biopharma are each conducting Phase 3 clinical trials with osilodrostat and levoketoconazole, respectively. Other companies developing products for potential use in Cushing's disease include Corcept, Cyclacel Pharmaceuticals, Inc. and Millendo Therapeutics, Inc. Neurocrine Biosciences and Spruce Biosciences are developing CRF receptor antagonists for the treatment of CAH.

With respect to CHI, 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. Xeris Pharmaceuticals, Inc. received marketing approval for its ready-to-use glucagon in 2019. Companies in or entering Phase 3 are Eli Lilly and Company and Zealand Pharma A/S with glucagon analogs. Other companies developing products for potential use in CHI include Eiger Biopharmaceuticals, Inc. and Rezolute, Inc.

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 strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to our business, including seeking, maintaining and defending our patent rights. We own the issued patents and patent applications relating to our lead product candidate paltusotine, as well as our other product candidates. Our policy is to seek to protect our proprietary position by, among other methods, filing patent applications in the United States and in jurisdictions outside of the United States directed to our proprietary technology, inventions, improvements and product candidates that are important to the development and implementation of our business. We also rely on trade secrets and know-how relating to our proprietary technology and product candidates and continuing innovation to develop, strengthen and maintain our proprietary position in the field of endocrinology. We also plan to rely on data exclusivity, market exclusivity and patent term extensions when available. Our commercial success will depend in part on our ability to obtain

and maintain patent and other proprietary protection for our technology, inventions and improvements; to preserve the confidentiality of our trade secrets; to defend and enforce our proprietary rights, including any patents that we may own in the future; and to operate without infringing on the valid and enforceable patents and other proprietary rights of third parties.

We own six U.S. patents. More specifically, we own two U.S. patents with claims directed to our lead product candidate paltusotine and other related compounds, as a composition of matter, as well as claims directed to pharmaceutical compositions and uses of such compounds, including the use of paltusotine, to treat acromegaly, neuroendocrine tumors, and/or pain. These U.S. patents are expected to expire in July 2037, absent any patent term extensions for regulatory delay. The other patents and patent applications are directed to various compounds as compositions of matter, pharmaceutical compositions comprising such compounds, and related methods of using such compounds. These issued patents, and any patents that may issue from our pending patent applications are expected to expire between 2036 and 2039, absent any 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. We also own three trademark registration applications.

With respect to our product candidates and processes we intend to develop and commercialize in the normal course of business, we intend to pursue patent protection covering, when possible, compositions, methods of use, dosing and formulations. We may also pursue patent protection with respect to manufacturing and drug development processes and technologies.

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 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 restoration period cannot be longer than five years and the total patent term, including the restoration 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 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.

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 field of endocrinology 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.

In addition, 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 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. 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 in certain circumstances. 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.

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.

Sales and marketing

We intend to build the commercial infrastructure in major markets 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 commercial infrastructure for orphan products typically consists of a targeted, specialty sales force that calls on a focused group of physicians supported by sales management, medical liaisons, 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 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, 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;
- 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 GMP, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Once a pharmaceutical 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 the IND. The sponsor will also include a protocol detailing, among other things, the objectives of the first phase of the clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated, if the first phase lends itself to 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. They 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 timely safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events. An 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.

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. Sponsors sometimes designate their Phase 1 clinical trials as Phase 1a or Phase 1b. Phase 1b clinical trials are typically aimed at confirming dosing, pharmacokinetics and safety in larger number of patients. Some Phase 1b studies evaluate biomarkers or surrogate markers that may be associated with efficacy in patients with specific types of diseases.
- *Phase 2:* This phase involves clinical trials in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and appropriate dosage.
- *Phase 3:* Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population, generally at geographically dispersed clinical study sites. These clinical trials are intended to establish the overall risk-benefit ratio of the product candidate and provide, if appropriate, 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.

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.

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.

While the IND is active and before approval, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report 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.

There are also requirements governing the reporting of ongoing clinical trials and completed trial results to public registries. Sponsors of certain clinical trials of FDA-regulated products are required to register and disclose specified clinical trial information, which is publicly available at www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, trial sites and investigators and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved.

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 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 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.

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. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. 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, it will issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A Complete Response Letter usually describes the specific deficiencies in the NDA identified by the FDA and may require additional clinical data, such as an additional pivotal Phase 3 trial or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter 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. Marketing approval may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

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 indication 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 one of our product candidates for seven years if a competitor obtains approval of the same drug as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. 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. With regard to a fast track product, 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.

Any product submitted to the FDA for approval, including a product with a fast track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval.

A product is eligible for priority review if it 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 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 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 may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. Drugs receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required post-marketing trials 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.

The Food and Drug Administration Safety and Innovation Act, or FDASIA, established a category of drugs referred to as "breakthrough therapies" that may be eligible to receive breakthrough therapy designation. A sponsor may seek FDA designation of a product candidate as a "breakthrough therapy" if the product is intended, alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically 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. The Breakthrough Therapy designation is a distinct status from both accelerated approval and priority review, which can also be granted to the same drug if relevant criteria are met. If a product is designated as breakthrough therapy, the FDA will work to expedite the development and review of such drug.

Fast Track designation, priority review and Breakthrough Therapy do not change the standards for approval but may expedite the development or approval process. Even if a product 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. We may explore some of these opportunities for our product candidates as appropriate.

Post-approval requirements

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. After approval, some types of 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. In addition, the FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

Any drug products manufactured or distributed by us or our partners pursuant to FDA approvals will be subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the drug, providing the FDA with updated safety and efficacy information, drug sampling and distribution requirements, complying with certain electronic records and signature requirements, and complying with FDA promotion and advertising requirements. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market and imposes requirements and restrictions on drug manufacturers, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. 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 or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds on post-approval clinical trials, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of

government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties.

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 marketing 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 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. In addition, orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances.

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 extends 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 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. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole."

Some of the provisions of the ACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA. For example, President Trump has signed Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or the Tax Act, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit affirmed the District Court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. It is unclear how these decisions, subsequent appeals, if any, or other efforts to repeal, challenge or replace the ACA will impact the ACA or our business.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of Medicare providers. 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., Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. 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.

On May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or Right to Try Act, was signed into law. The law, among other things, provides a federal framework for patients to access certain investigational new drug products that have completed a Phase I clinical trial. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA approval under the FDA expanded access program. The Right to Try Act did not establish any new entitlement or positive right to any party or individual, nor did it create any new mandates, directives, or additional regulations requiring a manufacturer or sponsor of an eligible investigational new drug product to provide expanded access.

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, data privacy and security, and transparency laws and regulations.

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 and the civil monetary penalties statute.

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. In addition, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes certain requirements relating to the privacy, security and transmission of protected health information on HIPAA covered entities, which include certain healthcare provider, health plans and healthcare clearinghouses, and their business associates who conduct certain activities involving protected health information on their behalf.

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 other healthcare professionals beginning in 2022, 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; and state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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.

Employees

As of February 28, 2020, we had 68 full-time employees, 20 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.

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. 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 two of our product candidates, paltusotine and CRN01941, 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 clinical trials beyond Phase 1, 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, 2019, we had an accumulated deficit of $93.8 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 and CRN01941 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 our ACTH antagonist and sst5 agonist development programs. 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 expect 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 or other sources, such as strategic collaborations. We do not currently expect future grant revenues to be a material source of 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 $75.0 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; and
- costs associated with any products or technologies that we may in-license or acquire.

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. 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.

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, including 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 two 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 two product candidates, paltusotine and CRN01941, 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 early 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 moving our other product candidates from preclinical studies into clinical development, including for our ACTH antagonist and sst5 agonist programs, discovering additional product candidates, 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 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 Phase 1 results for paltusotine, we do not know how paltusotine will perform in future clinical trials, including as a result of any differences resulting from the use of new formulations that we may use in subsequent 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. In addition, results from our Phase 1 clinical trial for paltusotine showed that the current capsule formulation exhibited an approximately 85% reduction in plasma concentrations when administered with a high fat breakfast, and, as a result, our protocols for our Phase 2 trials require that patients fast prior to drug therapy. This may introduce variability into our Phase 2 results due to patient compliance. We expect to conduct additional activities to improve the capsule formulation but cannot provide any assurance we will be successful in doing so. 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 we can initiate clinical trials for our product candidates, we must submit the results of preclinical studies to the FDA or comparable foreign regulatory authorities along with other information, including information about product candidate chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND or similar regulatory filing.

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. We conducted our Phase 1 clinical trial of paltusotine in Australia, and we submitted an IND to the FDA in August 2018 prior to initiating our Phase 2 clinical trials in late 2018. Our Phase 2 clinical trials are being conducted at centers in the United States, South America, Australia, New Zealand, as well as in certain European countries. In addition, our Phase 1 clinical trial of CRN01941 is currently being conducted in Australia. We may conduct future Phase 1 clinical trials for our other product candidates outside the United States. 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. Any 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.

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.

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 relevant to such foreign countries.

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.

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 25,000 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 ongoing clinical trials. For example, the most common adverse events observed in our Phase 1 trial of paltusotine were mild gastrointestinal disorders occurring in approximately 30% of subjects (such as abdominal pain, flatulence, abdominal distension, and diarrhea) and mild elevations of pancreatic enzymes occurring 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 non-sustained 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 by the investigator unlikely to be related to paltusotine. Further analysis may reveal adverse events inconsistent with the safety results observed to date. Additionally, while we have not yet initiated clinical trials for any of our other product candidates, it is likely that there may be side effects associated with their use. 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, 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.

Although we have completed our first Phase 1 clinical trial for paltusotine, we have not as an organization completed later-stage clinical trials or submitted an NDA and may be unable to do so for any of our product candidates.

We will need to successfully complete Phase 1 and Phase 2 clinical trials and later-stage and pivotal clinical trials in order to obtain FDA or comparable foreign regulatory approval to market paltusotine, CRN01941 or any of our other product candidates. Carrying out later-stage clinical trials and the submission of a successful NDA is a complicated process. As an organization, we are in the process of conducting our first Phase 2 clinical trials for paltusotine as well as a Phase 1 clinical trial for CRN01941 and have not yet conducted any clinical trials for our other product candidates. We have not previously conducted any later stage or pivotal clinical trials, have limited experience in preparing and submitting regulatory filings and have not previously submitted an NDA or other comparable foreign regulatory submission for any product candidate. In addition, we have had limited interactions with the FDA and cannot be certain how many additional clinical trials of paltusotine, CRN01941 or any of our other product candidates will be required or how such trials should be designed. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to regulatory submission and approval of paltusotine, CRN01941 or any of our other product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing paltusotine, CRN01941 or any other product candidate.

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. 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 plan to seek orphan drug designation for paltusotine and certain of our other product candidates. 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 European Medicines Agency's, or the EMA, 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 plan to seek orphan drug designation in the United States and the European Union for paltusotine for acromegaly patients, and we intend to seek orphan drug designation for certain of our other product candidates. There can be no assurance 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 indication 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.

We have conducted, and continue to conduct, clinical trials for paltusotine and CRN01941 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 conducted our initial Phase 1 clinical trials for paltusotine in Australia and we are conducting our Phase 2 clinical trials for paltusotine at centers in the United States, South America, Australia, New Zealand, and in certain European countries. In addition, our Phase 1 clinical trial of CRN01941 is currently being conducted in Australia. We believe that clinical data generated outside of the United States will be accepted by the FDA and its foreign equivalents outside, and therefore will enable us to commence registration clinical trials in the United States or the European Union, without the need for us to repeat our Phase 1 and Phase 2 clinical trials. If the FDA, U.K. Medicines and Healthcare Products Regulatory Agency, or MHRA, or other foreign equivalents do not accept any such data, 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.

Although the FDA, MHRA and other foreign equivalents may accept data from clinical trials conducted entirely outside the United States and not under an IND, acceptance of such study data is generally subject to certain conditions. For example, the

FDA requires the clinical trial to have been conducted in accordance with GCPs, and the FDA must be able to validate the data from the clinical trial through an onsite inspection if it deems such inspection necessary. In addition, when studies are conducted only at sites outside of the United States, the FDA generally does not provide advance comment on the clinical protocols for the studies, and therefore there is an additional potential risk that the FDA could determine that the study design or protocol for a non-U.S. clinical trial was inadequate, which would likely require us to conduct additional clinical trials.

Conducting clinical 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; and
- diminished protection of intellectual property in some countries.

For example, effective January 31, 2020, the United Kingdom commenced an exit from the European Union, commonly referred to as "Brexit." During a transition period (set to expire on December 31, 2020), the British government will continue to negotiate the terms of the United Kingdom's future relationship with the European Union. The outcome of these negotiations is uncertain, and we do not know to what extent Brexit will ultimately impact the business and regulatory environment in the United Kingdom, the rest of the EU, or other countries. This could cause disruptions to, and create uncertainty surrounding, our planned clinical trials and activities in the United Kingdom, including affecting our relationships with our existing and prospective customers, partners, vendors and employees, and could have a material impact on the regulatory regime applicable to our planned clinical trial in the United Kingdom. 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 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. 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, 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 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 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 ongoing clinical trials for paltusotine and CRN01941 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. 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.

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. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, and we may not achieve or sustain profitability.

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. For example, certain policies of the current U.S. administration may impact our business and industry. Namely, the current U.S. administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these executive actions, including the Executive Orders, will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Changes in funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed or commercialized in a timely manner, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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 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). 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 terms of other products in clinical development, all of them are new formulations of peptide somatostatin agonists or GH receptor antagonists. Chiasma, Inc. has submitted an NDA to the FDA for an oral octreotide product candidate for the maintenance therapy of adult patients with acromegaly in whom prior treatment with somatostatin analogs has been shown to be effective and tolerated. Other companies developing new pharmaceutical therapies for acromegaly include Camurus AB, Dauntless Pharmaceuticals, Inc., Enesi Pharma Limited, Ionis Pharmaceuticals, Inc./Antisense Therapeutics Ltd., MidaTech Pharma PLC, Aquestive Therapeutics, Inc. 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 Lexicon Pharmaceuticals, Inc.) is an orally administered add-on therapy. Targeted therapies everolimus (marketed by Novartis) and sunitinib malate (marketed by Pfizer) are typically only used in patients with high grade tumors which constitute only a small fraction of NETs. In 2018, the FDA approved Novartis' Lutathera for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors. Companies in Phase 3 development include Progenics Pharmaceuticals, Inc. and EUSA Pharma Inc. Other companies developing products for potential use in NETs include Apeiron Scientific, LLC, Camurus, Celgene Corporation, EpicentRx, Inc., Ipsen, Mateon Therapeutics, Inc., Merck & Co., Inc., MidaTech, Novartis, Oncoceutics, Inc. and Roche Holding AG.

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. The somatostatin agonist pasireotide is also approved for Cushing's disease. Recordati and Strongbridge Biopharma are each conducting Phase 3 clinical trials with osilodrostat and levoketoconazole, respectively. Other companies developing products for potential use in Cushing's disease include Corcept, Cyclacel Pharmaceuticals, Inc. and Millendo Therapeutics, Inc. Neurocrine Biosciences and Spruce Biosciences are developing CRF receptor antagonists for the treatment of CAH.

With respect to CHI, 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 and lanreotide (used off-label) are administered as injections in patients 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. Xeris Pharmaceuticals, Inc. received marketing approval for its ready-to-use glucagon in 2019. Companies in or entering Phase 3 are Eli Lilly and Company and Zealand Pharma A/S with glucagon analogs. Other companies developing products for potential use in CHI include Eiger Biopharmaceuticals, Inc. and Rezolute, Inc.

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, including acromegaly, NETs, Cushing's Disease, CAH, EAS and CHI 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, any future collaboration agreements 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 28, 2020, we had 68 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 Anti- Kickback 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;
- the federal Health Insurance Portability and Accountability Act of 1996, or 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 (starting in 2022), 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.

We are subject to governmental regulation and other legal obligations related to privacy, data protection and information security. Compliance with these requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data, and the failure to comply with such 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. As we receive, collect, process, use and store personal and confidential data, we are subject to diverse laws and regulations relating to data privacy and security, including, in the U.S., HIPAA and CCPA (defined below), and, in the E.U., and shortly in the EEA, Regulation 2016/679, known as the General Data Protection Regulation, or GDPR. 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, or HITECH, and their respective implementing regulations, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. Among other things, HITECH made HIPAAs security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity, although we believe that we would not be considered a "business associate" in the normal course of our business. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. Even when HIPAA does not apply, according to the Federal Trade Commission or the FTC, failing to take appropriate steps to keep consumers' personal information secure constitutes unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act, or the FTCA, 15 U.S.C § 45(a). The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Individually identifiable health information is considered sensitive data that merits stronger safeguards. The FTC's guidance for appropriately securing consumers' personal information is similar to what is required by the HIPAA security regulations.

In addition, state laws govern the privacy and security of health 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, 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 is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.

In Europe, as of May 25, 2018, the General Data Protection Regulation, or GDPR replaced the Data Protection Directive with respect to the processing of personal data in the European Union. The GDPR imposes many requirements for controllers and processors of personal data, including, for example, higher standards for obtaining consent from individuals to process their personal data, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention and secondary use of information, increased requirements pertaining to health data and pseudonymized (i.e., key-coded) data and additional obligations when we contract third-party processors in

connection with the processing of the personal data. The GDPR allows EU member states to make additional laws and regulations further limiting the processing of genetic, biometric or health data. Failure to comply with the requirements of GDPR and the applicable national data protection laws of the EU member states may result in fines of up to €20,000,000 or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, and other administrative penalties. Additionally, following the United Kingdom's withdrawal from the European Union, we will have to comply with the GDPR and the United Kingdom GDPR, each regime having the ability to fine up to the greater of €20 million/ £17.5 million or 4% of global turnover. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, for example around how data can lawfully be transferred between each jurisdiction, which exposes us to further compliance risk.

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: establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; expands eligibility criteria for Medicaid programs; increases the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program; creates a new Medicare Part D coverage gap discount program; establishes 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 establishes 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. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole."

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA and we expect such challenges and amendments to continue. For example, the Tax Act includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit affirmed the District Court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. It is unclear how these decisions, subsequent appeals and other efforts to challenge, repeal or replace the ACA will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, included reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2029 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.

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. Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

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.

On May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or Right to Try Act, was signed into law. The law, among other things, provides a federal framework for patients to access certain investigational new drug products that have completed a Phase I clinical trial. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA approval under the FDA expanded access program. The Right to Try Act did not establish any new entitlement or positive right to any party or individual, nor did it create any new mandates, directives, or additional regulations requiring a manufacturer or sponsor of an eligible investigational new drug product to provide expanded access.

We expect that the ACA, 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.

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.

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. Claims could also 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 internal computer 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.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to damage from computer viruses, cybersecurity threats, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our 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.

The implementation of a new accounting system could interfere with our business and operations.

We are in the process of implementing a new accounting system, NetSuite. The implementation of new systems and enhancements may be disruptive to our business and can be time-consuming and divert management's attention. Any disruptions relating to our systems or any problems with the implementation, particularly any disruptions impacting our operations or our ability to accurately report our financial performance on a timely basis during the implementation period, could materially and adversely affect our business and operations.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to 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. For example, in December 2019, a novel strain of coronavirus was reported to have surfaced in Wuhan, Hubei Province, China, resulting in the closure of certain of our third-party manufacturers and clinical suppliers. While these closures are expected to be temporary, the

continued closure or understaffing of these vendors could delay our ability to conduct and/or complete our ongoing preclinical studies in a timely fashion. At this point, the extent to which the coronavirus, and any measures taken by the governments of China or any of the other countries affected, may impact our results is uncertain and cannot be predicted. 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.

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 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.

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.

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.

Although we own six issued patents in the United States, we cannot be certain that the claims in our other U.S. pending patent applications, corresponding international patent applications and patent applications in certain foreign territories will be considered patentable by the United States Patent and Trademark Office, or USPTO, courts in the United States or by the patent offices and courts in foreign countries, nor can we be certain that the claims in our issued patents will not be found invalid or unenforceable if challenged.

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.

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 generally is 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 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.

Most 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 our 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, 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.

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.

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 patents and 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 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 on such product candidate. 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 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.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a "first inventor to file" system in which, assuming that other requirements of patentability are met, the first inventor to file a patent application will be entitled to the patent regardless of whether a third party was first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013 but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Furthermore, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we were the first to either (1) file any patent application related to our product candidates or (2) invent any of the inventions claimed in our patents or patent applications.

The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including PGR, IPR, and derivation proceedings. An adverse determination in any such submission or proceeding could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Thus, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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.

Although we have six issued patents in the United States and pending patent applications in the United States and other countries, filing, prosecuting and defending patents in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. 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. 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.

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, our registered or unregistered trademarks or trade names may 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 only 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 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 other events or factors, many of which are beyond our control;
- 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 80% of our outstanding common stock as of February 28, 2020. 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 12,398,097 shares of our outstanding common stock, or approximately 50% of our total outstanding common stock as of February 28, 2019, 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.

We are an emerging growth company and a smaller reporting company, and the reduced disclosure requirements applicable to such companies may make our common stock less attractive to investors.

We are an emerging growth company, as defined in the JOBS Act, and a smaller reporting company, as defined under the rules promulgated under the Securities Act. We may remain an emerging growth company until the last day of the fiscal year following the fifth anniversary of the completion of our initial public offering, or IPO. However, if certain events occur prior to the end of such five-year period, including if we become a “large accelerated filer,” our annual gross revenues exceed $1.07 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a smaller reporting company, and we will remain a smaller reporting company until the fiscal year following the determination that our voting and non-voting common shares held by non-affiliates is more than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are more than $100 million during the most recently

completed fiscal year and our voting and non-voting common shares held by non-affiliates is more than $700 million measured on the last business day of our second fiscal quarter. Similar to emerging growth companies, smaller reporting companies are able to provide simplified executive compensation disclosure and have certain other reduced disclosure obligations, including, among other things, being required to provide only two years of audited financial statements and not being required to provide selected financial data, supplemental financial information or risk factors.

We may choose to take advantage of some, but not all, of the available exemptions for emerging growth companies and smaller reporting companies. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be reduced or more volatile.

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 that we did not incur as a private company. 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 will apply to us when we cease to be an emerging growth company. 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 may substantially 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, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required 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. When we lose our status as an "emerging growth company," unless we are no longer an accelerated filer, our independent registered public accounting firm will be 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 are in process of implementing additional financial and management controls, reporting systems and procedures; and hiring additional accounting and finance staff. If we or, if required, 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, 2019, 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 once that firm begin its Section 404 reviews, 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.

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, 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. This provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees,

which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find 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 and do not expect to become profitable in the near future, and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire (if at all). At December 31, 2019, after reducing net operating losses, or NOLs, and research and development credits for amounts not expected to be utilized, we had federal, state and foreign NOL carryforwards of approximately $54.5 million, $61.6 million and $0.4 million, respectively. The federal and state NOL carryforwards will begin to expire in 2035, unless previously utilized. The foreign NOL carryforwards do not expire. The Company also has federal and California research and development credit carryforwards totaling $4.0 million and $1.9 million, respectively. The federal research and development credit carryforwards will begin to expire in 2030, unless previously utilized. The California research credits do not expire.

Under recently enacted U.S. tax legislation, federal NOL carryforwards generated in periods after December 31, 2017, may be carried forward indefinitely but may only be used to offset 80% of our taxable income annually. The California research and development tax carryforwards are available indefinitely. Our NOL carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities and may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50 percentage points, as defined under Section 382 of the Internal Revenue Code of 1986, as amended. Our ability to utilize our NOL carryforwards and other tax attributes to offset future taxable income or tax liabilities may be limited as a result of ownership changes, including potential changes in connection with our IPO or future offerings. Similar rules may apply under state tax laws. We have not yet determined the amount of the cumulative change in our ownership resulting from our IPO or any resulting tax loss limitations. Such limitations could result in the expiration of our carryforwards before they can be utilized and, if we are profitable, our future cash flows could be adversely affected due to our increased tax liability. We have recorded a full valuation allowance related to our NOLs and other deferred tax assets due to the uncertainty of the ultimate realization of the future benefits of those assets.

Changes in U.S. tax law may materially adversely affect our financial condition, results of operations and cash flows.

The Tax Cut and Jobs Act of 2017 has significantly changed the U.S. federal income taxation of U.S. corporations. The Tax Act remains unclear in many respects and has been, and may continue to be, the subject of amendments and technical corrections, as well as interpretations and implementing regulations by the Treasury and Internal Revenue Service, which have lessened or increased certain adverse impacts of the Tax Act and may do so in the future. In addition, it is unclear how these U.S. federal income tax changes will affect state and local taxation, which often uses federal taxable income as a starting point for computing state and local tax liabilities. We continue to work with our tax advisors and auditors to determine the full impact the Tax Act will have on us. We urge our investors to consult with their legal and tax advisors with respect to the Tax Act.

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, with the option to extend the term of the lease for an additional five years, subject to certain conditions.

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 28, 2020, there were 19 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.

Recent Sales of Unregistered Securities

None.

Use of Proceeds

On July 17, 2018, the SEC declared effective our registration statement on Form S-1 (File No. 333-225824), as amended, filed in connection with our IPO. The IPO closed on July 20, 2018 and we issued and sold 6,900,000 shares of our common stock at a price to the public of $17.00 per share, which included the exercise in full of the underwriters' option to purchase additional shares. We received gross proceeds from the IPO of $117.3 million, before deducting underwriting discounts and commissions of approximately $8.2 million and estimated offering expenses of approximately $2.6 million. The managing underwriters of the offering were J.P. Morgan Securities LLC, Leerink Partners LLC and Piper Jaffray & Co. No offering expenses were paid or are payable, directly or indirectly, to our directors or officers, to persons owning 10% or more of any class of our equity securities or to any of our affiliates. There has been no material change in the planned use of such proceeds from that described in the prospectus for our IPO.

As of December 31, 2019, we have not used any of the proceeds from our IPO.

Issuer Repurchases of Equity Securities

None.

Stock Performance Graph

The following graph shows a comparison from July 18, 2018 (the date our common stock commenced trading on the Nasdaq Global Select Market) through December 31, 2019 of the cumulative total return for our common stock, the Nasdaq Biotechnology Index (NBI) and the Nasdaq Composite index (IXIC). The graph assumes an initial investment of $100 on July 18, 2018. The comparison in the graph is not intended to forecast or be indicative of the possible future performance of our common stock.

Item 6. Selected Financial Data

The following selected financial data has been derived from our audited consolidated financial statements. This data should be read in conjunction with Item 7 — "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes thereto included elsewhere in this Form 10-K. Our historical results are not necessarily indicative of operating results to be expected in the future.

	Year ended December 31,			
Amounts in thousands, except per share data:	**2019**	**2018**	**2017**	**2016**
Statement of operations data:				
Grant revenues	$ 1,193	$ 2,428	$ 2,045	$ 589
Research and development expenses	$ 41,506	$ 24,479	$ 9,233	$ 5,100
General and administrative expenses	$ 13,519	$ 6,659	$ 1,939	$ 1,533
Total operating expenses	$ 55,025	$ 31,138	$ 11,172	$ 6,633
Loss from operations	$ (53,832)	$ (28,710)	$ (9,127)	$ (6,044)
Net loss	$ (50,422)	$ (27,115)	$ (9,157)	$ (6,019)
Net loss per share – basic and diluted	$ (2.09)	$ (2.23)	$ (6.68)	$ (5.96)
Weighted average shares outstanding – basic and diluted	24,175	12,142	1,371	1,011

	Year ended December 31,			
Amounts in thousands:	**2019**	**2018**	**2017**	**2016**
Balance sheet data:				
Cash, cash equivalents and short-term investments	$ 118,392	$ 163,875	$ 14,192	$ 12,152
Working capital	$ 114,999	$ 158,758	$ 14,268	$ 11,475
Total assets	$ 130,377	$ 171,415	$ 15,598	$ 12,599
Total liabilities	$ 13,238	$ 11,190	$ 920	$ 1,063
Convertible preferred stock	$ —	$ —	$ 29,700	$ 17,740
Accumulated deficit	$ (93,802)	$ (43,380)	$ (16,265)	$ (7,108)
Total stockholders' equity (deficit)	$ 117,139	$ 160,225	$ (15,022)	$ (6,204)

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.

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 assembled a seasoned team with extensive expertise in drug discovery and development in endocrine GPCRs and built a highly productive drug discovery organization. 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 lead product candidate, paltusotine (formerly CRN00808), is currently in clinical development for the treatment of acromegaly, and we are advancing additional product candidates through clinical and preclinical 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 two product candidates and preclinical programs:

- Paltusotine, our lead product candidate, establishes a new class of oral selective nonpeptide somatostatin receptor type 2, or sst2, biased agonists designed for the treatment of acromegaly and neuroendocrine tumors, or NETs. We are currently conducting three global Phase 2 clinical trials of paltusotine in acromegaly patients, the ACROBAT EVOLVE, or EVOLVE, ACROBAT EDGE, or EDGE and ACROBAT ADVANCE, or ADVANCE, trials. The EVOLVE trial is a double-blind, placebo-controlled, randomized withdrawal study designed to evaluate the safety, efficacy and pharmacokinetics of paltusotine, in subjects with acromegaly whose disease is biochemically controlled by octreotide LAR or lanreotide depot monotherapy. The EDGE trial is an open label exploratory study designed to evaluate the safety, efficacy and pharmacokinetics of paltusotine in subjects with acromegaly that are treated with somatostatin analog based treatment regimens but whose disease is not biochemically controlled by monotherapy. The ADVANCE trial is an open label, long term extension study designed to evaluate the safety and efficacy of paltusotine in patients that have completed the EVOLVE or EDGE trials. We dosed the first patients in the EVOLVE and EDGE trials in March 2019.
- CRN01941 is also an oral nonpeptide sst2 biased agonist initially in development for the treatment of NETs. We initiated a Phase 1 clinical trial in May 2019 to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of CRN01941 and expect results from this trial in early 2020. We intend to decide whether to advance CRN01941 or paltusotine into a later stage trial in NETs upon analysis of the cumulative data from the paltusotine and CRN01941 preclinical, nonclinical and clinical programs.
- We are developing the first nonpeptide product candidate to antagonize peptide adrenocorticotrophic hormone, or ACTH, designed for the treatment of Cushing's disease and other diseases caused by excess ACTH, including congenital adrenal hyperplasia and Ectopic ACTH Syndrome. We are currently conducting first-in-human enabling studies with our lead ACTH antagonist development candidate.
- We are developing a new class of oral selective nonpeptide somatostatin type 5 receptor, or sst5, agonists designed to treat congenital hyperinsulinism, or CHI. We are currently conducting first-in-human enabling studies with our lead sst5 agonist development candidate.

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, and the provision of general and administrative support for these operations. We recognize revenues from various research and development grants, but do not have any products approved for sale and have not generated any product sales. We have funded our operations to date primarily through our grant revenues, the private placement of our preferred stock, and our initial public offering, or IPO, in July 2018. As of December 31, 2019, we had unrestricted cash, cash equivalents and investment securities of $118.4 million.

We have incurred cumulative net losses since our inception and, as of December 31, 2019, we had an accumulated deficit of $93.8 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.

Financial operations overview

Grant revenues

To date, 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. Revenues for 2019, 2018 and 2017 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. We do not currently expect future grant revenues to be a material source of 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 non-clinical 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 2019, 2018 and 2017 related to the research and development of paltusotine. 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 Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of these 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 related to revenue recognition, accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that we believe are reasonable under the circumstances, 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.

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.

Australian research and development tax incentive

CAPL is eligible to obtain a cash refund from the Australian Taxation Office for eligible research and development expenditures under the Australian Tax Incentive. The Australian Tax Incentive is recognized as a reduction to research and development expense when there is reasonable assurance that the Australian Tax Incentive will be received, the relevant expenditure has been incurred, and the amount can be reliably measured. Although we do not expect our estimates to be materially different from amounts actually received, if our estimates of the amounts and timing of the receipt of the Australian Tax Incentive differ from actual amounts received, it could result in us reporting amounts that are too high or too low in any particular period.

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.

Operating Lease

Effective January 1, 2019, 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 assets, accrued expenses and other current liabilities and noncurrent operating lease liabilities in the consolidated balance sheets based on the present value of the minimum lease payments called for under the arrangement. Lease expense for minimum lease payments is recognized on a straight-line basis over the lease term.

Stock-based compensation expense

Stock-based compensation expense represents the cost of the estimated grant date fair value of stock option awards and employee stock purchase plan rights amortized over the requisite service period of the awards (usually the vesting period) on a straight-line basis. We estimate the fair value of all stock option grants using the Black-Scholes option pricing model and recognize forfeitures as they occur.

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, 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 a sufficient amount of historical information regarding the volatility of our common stock price becomes available. 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 risk-free interest rates for periods within the expected life of the option are based on the yields of zero-coupon U.S. treasury securities.

Results of Operations

Comparison of the years ended December 31, 2019 and 2018.

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018 (*in thousands*):

	Year ended December 31,		Dollar
	2019	2018	Change
Grant revenues	$ 1,193	$ 2,428	$ (1,235)
Operating expenses:			
Research and development	41,506	24,479	17,027
General and administrative	13,519	6,659	6,860
Total operating expenses	55,025	31,138	23,887
Loss from operations	(53,832)	(28,710)	(25,122)
Other income (expense), net	3,410	1,595	1,815
Net loss	$ (50,422)	$ (27,115)	$ (23,307)

Grant revenues. Grant revenues relate to reimbursable expenses incurred in connection with our SBIR Grants and totaled $1.2 million and $2.4 million for the years ended December 31, 2019 and 2018, respectively. Our 2019 revenues were primarily associated with research activities for one SBIR Grant, while our 2018 revenues were primarily related to research activities for two such grants. We do not expect grant revenues to be significant in future periods.

Research and development expenses. Research and development expenses were $41.5 million and $24.5 million for the years ended December 31, 2019 and 2018, respectively. The increase was primarily due to increased spending on manufacturing and development activities of $9.9 million associated with our clinical and nonclinical activities for paltusotine as well as our other clinical and preclinical programs. Additionally, our 2019 results reflect an increase in costs of $4.5 million due to the hiring of additional personnel (which includes $2.1 million of additional stock-based compensation).

General and administrative expenses. General and administrative expenses were $13.5 million and $6.7 million for the years ended December 31, 2019 and 2018, respectively. The increase was primarily due to increases in personnel-related costs of $3.2 million (which includes $1.9 million of additional stock-based compensation), spending on pre-commercialization activities and corporate legal services of $1.6 million, as well as expenses associated with operating as a publicly traded company.

Other income (expense). Other income (expense), net was $3.4 million and $1.6 million for the years ended December 31, 2019 and 2018, respectively. The increase was primarily due to interest income earned on higher cash and investment balances due to the funds raised from investors in 2018.

Comparison of the years ended December 31, 2018 and 2017.

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017 (*in thousands*):

	Year ended December 31,		Dollar
	2018	2017	Change
Grant revenues	$ 2,428	$ 2,045	$ 383
Operating expenses:			
Research and development	24,479	9,233	15,246
General and administrative	6,659	1,939	4,720
Total operating expenses	31,138	11,172	19,966
Loss from operations	(28,710)	(9,127)	(19,583)
Other income (expense), net	1,595	(30)	1,625
Net loss	$ (27,115)	$ (9,157)	$ (17,958)

Grant revenues. Grant revenues were $2.4 million and $2.0 million for the years ended December 31, 2018 and 2017, respectively. The increase was primarily due to an increase in reimbursable research and development expenses under our SBIR Grants during 2018.

Research and development expenses. Research and development expenses were $24.5 million and $9.2 million for the years ended December 31, 2018 and 2017, respectively. The increase was primarily due to increased spending on manufacturing and development activities associated with our clinical and nonclinical activities for paltusotine as well as our other preclinical programs, an increase in personnel related costs due to the hiring of additional development personnel, including $1.0 million of additional stock-based compensation, and increased facility costs due to the expansion of our leased facilities.

General and administrative expenses. General and administrative expenses were $6.7 million and $1.9 million for the years ended December 31, 2018 and 2017, respectively. The increase was primarily due to increases in personnel-related costs, including $1.1 million of additional stock-based compensation, as well as expenses associated with operating as a publicly traded company.

Other income (expense). Net other income was $1.6 million for the year ended December 31, 2018, compared with net other expense of $30,000 for the year ended December 31, 2017. The increase was primarily due to interest income earned on higher cash and investment balances due to the funds raised from investors in 2018.

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, 2019, we had an accumulated deficit of $93.8 million and unrestricted cash, cash equivalents and investment securities of $118.4 million.

The following table provides information regarding our cash flows for each of the years in the three-year period ended December 31, 2019 (*in thousands*):

	Years ended December 31,		
	2019	2018	2017
Net cash used in operating activities	$ (46,381)	$ (19,459)	$ (9,479)
Net cash provided by (used in) investing activities	41,667	(119,458)	(304)
Net cash provided by financing activities	67	170,198	11,823
Net change in cash, cash equivalents and restricted cash	$ (4,647)	$ 31,281	$ 2,040

Comparison of the years ended December 31, 2019 and 2018

Operating Activities. Net cash used in operating activities was $46.4 million and $19.5 million for the years ended December 31, 2019 and 2018, respectively. The increase in cash used in operations was primarily attributable to development and manufacturing activities associated with paltusotine as well as our other clinical and preclinical programs, and higher personnel-related costs. The net cash used in operating activities during the year ended December 31, 2019 was primarily due to our net loss of $50.4 million and a $2.1 million change in operating assets and liabilities, adjusted for $6.2 million of noncash charges, including stock-based compensation and depreciation expense. Net cash used in operating activities during the year ended December 31, 2018 was primarily due to our net loss of $27.1 million, adjusted for $2.4 million of noncash charges, primarily for stock-based compensation and depreciation expense, and a $5.3 million change in 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 a net inflow of funds of approximately $41.7 million during 2019, compared to approximately $119.5 million used during 2018.

Financing activities. Net cash provided by financing activities was $67,000 and $170.2 million for the years ended December 31, 2019 and 2018, respectively. The net cash provided by financing activities during 2019 was the result of the exercise of stock options, net of stock repurchase activities. The net cash provided by financing activities during 2018 was primarily due to the net proceeds of $63.3 million from the sale of Series B convertible preferred stock, the net proceeds of $106.5 million raised in our initial public offering in July and $0.5 million from the exercise of common stock options.

Comparison of the years ended December 31, 2018 and 2017

Operating Activities. Net cash used in operating activities was $19.5 million and $9.5 million for the years ended December 31, 2018 and 2017, respectively. The net cash used in operating activities during the year ended December 31, 2018 was primarily due to our net loss of $27.1 million, adjusted for $2.4 million of noncash charges and a $5.3 million change in operating assets and liabilities. The increase in cash used in operations were primarily attributable to development and manufacturing activities associated with paltusotine as well as our clinical and preclinical programs, and higher personnel costs. The noncash charges primarily related to $2.3 million of stock-based compensation charges and $0.5 million of depreciation expense. Net cash used in operating activities during the year ended December 31, 2017 was primarily due to our net loss of $9.2 million, adjusted for $0.4 million of noncash charges and a $0.7 million change in operating assets and liabilities. The noncash charges primarily related to $0.3 million of stock-based compensation charges and $0.1 million of depreciation expense.

Investing activities. Investing activities represent activity associated with our investment securities and, to a lesser extent, the cash outflow associated with purchases of property and equipment. Such activities resulted in a net use of funds of approximately $119.5 million during 2018, compared to approximately $0.3 million used during the same period in 2017.

Financing activities. Net cash provided by financing activities was $170.2 million for the year ended December 31, 2018, primarily due to the net proceeds of $63.3 million from the sale of Series B convertible preferred stock, the net proceeds of $106.5 million raised in our initial public offering in July and $0.5 million from the exercise of common stock options. Net cash provided by financing activities for the year ended December 31, 2017 was the result of net proceeds of $12.0 million from the sale of Series A convertible preferred stock and $0.1 million from the exercise of common stock options, offset by principal payments on an outstanding bank loan, which was repaid in full in 2017.

Liquidity and Capital Resources

We believe that our existing unrestricted cash, cash equivalents and investment securities, together with investment income, and future payments due under our SBIR Grants, will be sufficient to satisfy our current and projected funding requirements into the second half of 2021. We expect these funds will allow us to complete our ongoing Phase 2 clinical trials for paltusotine as well as continue advancing our pipeline programs. 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; and
- costs associated with any products or technologies that we may in-license or acquire.

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 having an aggregate offering price of up to $75.0 million through the Sales Agents. Sales of our common stock made pursuant to the Sales Agreement, if any, 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 19, 2019 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, 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. As of December 31, 2019, no shares had been issued pursuant to the Sales Agreement.

Between January 1, 2020 and March 6, 2020, the Company issued 275,764 shares of common stock in the ATM Offering for net proceeds of $6.4 million, after deducting commissions.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations at December 31, 2019 (in thousands):

	Payments due by period				
	Total	Less than 1 year	1 — 3 years	3 — 5 years	More than 5 years
Operating lease obligations (1)	$ 6,899	$ 1,123	$ 2,381	$ 2,524	$ 871
Total	$ 6,899	$ 1,123	$ 2,381	$ 2,524	$ 871

(1) Our operating lease obligations relate to our corporate headquarters in San Diego, California.

We enter into contracts in the normal course of business with clinical trial sites and clinical supply manufacturers and with vendors for preclinical studies, research supplies and other services and products for operating purposes. These contracts generally provide for termination after a notice period, and, therefore, are cancelable contracts and not included in the table above.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

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. We are therefore subject to fluctuations in foreign currency rates in connection with these agreements. We do not hedge our foreign currency exchange rate risk. 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 totaled approximately $50,000 and $144,000 for the years ended December 31, 2019 and 2018, respectively. As of December 31, 2019, the impact of a theoretical 10% change in the exchange rate of the Australian dollar would not result in a material gain or loss.

Inflation Risk

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation has had a material effect on our results of operations during the periods presented.

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 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, 2019, 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, 2019.

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, 2019, 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, 2019, our internal control over financial reporting was effective based on those criteria.

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, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

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 2019 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, 2019, 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.

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 report 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. and its subsidiary (the "Company") as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2019, 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 and its subsidiary at December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with accounting principles generally accepted in the United States of America.

Change in Accounting Principle

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Codification Topic 842, *Leases*.

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 Public Company Accounting Oversight Board (United States) ("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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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.

/s/ BDO USA, LLP

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

San Diego, California
March 9, 2020

CRINETICS PHARMACEUTICALS, INC.

Consolidated Balance Sheets
(In thousands)

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 40,326	$ 44,973
Investment securities	78,066	118,902
Prepaid expenses and other current assets	4,947	2,808
Total current assets	123,339	166,683
Property and equipment, net	3,946	4,232
Operating lease right-of-use asset	2,510	—
Restricted cash	500	500
Other assets	82	—
Total assets	$ 130,377	$ 171,415
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 5,498	$ 5,265
Accrued compensation and related expenses	2,118	2,279
Other current liabilities	724	381
Total current liabilities	8,340	7,925
Operating lease liability, non-current	4,849	—
Unvested stock liability	49	202
Deferred rent	—	3,063
Total liabilities	13,238	11,190
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Preferred stock, $0.001 par; 10,000 shares authorized, no shares issued or outstanding at December 31, 2019 or 2018	—	—
Common stock and paid-in capital, $0.001 par; 200,000 shares authorized, 24,296 and 24,263 shares issued and outstanding at December 31, 2019; 24,188 and 24,061 shares issued and outstanding at December 31, 2018	210,793	203,544
Accumulated other comprehensive income	148	61
Accumulated deficit	(93,802)	(43,380)
Total stockholders' equity	117,139	160,225
Total liabilities and stockholders' equity	$ 130,377	$ 171,415

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS

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

	Year ended December 31,		
	2019	**2018**	**2017**
Grant revenues	$ 1,193	$ 2,428	$ 2,045
Operating expenses:			
Research and development	41,506	24,479	9,233
General and administrative	13,519	6,659	1,939
Total operating expenses	55,025	31,138	11,172
Loss from operations	(53,832)	(28,710)	(9,127)
Other income (expense):			
Interest income	3,460	1,748	26
Other income (expense), net	(50)	(153)	(56)
Total other income (expense), net	3,410	1,595	(30)
Net loss	(50,422)	(27,115)	(9,157)
Other comprehensive income:			
Unrealized gain on investment securities	87	61	—
Comprehensive loss	$ (50,335)	$ (27,054)	$ (9,157)
Net loss per share:			
Net loss per share - basic and diluted	$ (2.09)	$ (2.23)	$ (6.68)
Weighted average shares - basic and diluted	24,175	12,142	1,371

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS, INC.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands)

	Convertible Preferred Stock		Common Stock	Common Stock and Paid-In	Accumulated Other	Accumulated	Total Stockholders'
	Shares	Amount	Shares	Capital	Comprehensive Income	Deficit	Equity (Deficit)
Balance at January 1, 2017	17,258	$ 17,740	1,165	$ 904	$ —	$ (7,108)	$ (6,204)
Issuance of Series A convertible preferred, net of issuance costs of $40	11,505	11,960	—	—	—	—	—
Vesting of shares subject to repurchase	—	—	287	2	—	—	2
Exercise of stock options	—	—	98	66	—	—	66
Stock-based compensation	—	—	—	271	—	—	271
Net loss	—	—	—	—	—	(9,157)	(9,157)
Balance at December 31, 2017	28,763	29,700	1,550	1,243	—	(16,265)	(15,022)
Issuance of Series B convertible preferred, net of issuance costs of $225	19,641	63,275	—	—	—	—	—
Issuance of common stock in initial public offering, net of issuance costs of $10,829	—	—	6,900	106,472	—	—	106,472
Conversion of preferred stock into common stock	(48,404)	(92,975)	14,713	92,975	—	—	92,975
Vesting of shares subject to repurchase	—	—	541	21	—	—	21
Exercise of stock options	—	—	337	231	—	—	231
Issuance of stock pursuant to Stock Purchase Plan	—	—	20	282	—	—	282
Stock-based compensation	—	—	—	2,320	—	—	2,320
Comprehensive income	—	—	—	—	61	—	61
Net loss	—	—	—	—	—	(27,115)	(27,115)
Balance at December 31, 2018	—	—	24,061	203,544	61	(43,380)	160,225
Vesting of shares subject to repurchase	—	—	63	94	—	—	94
Exercise of stock options	—	—	90	126	—	—	126
Issuance of stock pursuant to Stock Purchase Plan	—	—	49	735	—	—	735
Stock-based compensation	—	—	—	6,294	—	—	6,294
Comprehensive income	—	—	—	—	87	—	87
Net loss	—	—	—	—	—	(50,422)	(50,422)
Balance at December 31, 2019	—	$ —	24,263	$ 210,793	$ 148	$ (93,802)	$ 117,139

See the accompanying notes to these consolidated financial statements.

CRINETICS PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows
(In thousands)

	Year ended December 31,		
	2019	**2018**	**2017**
Operating activities:			
Net loss	$ (50,422)	$ (27,115)	$ (9,157)
Reconciliation of net loss to net cash used in operating activities:			
Stock-based compensation	6,294	2,320	271
Depreciation and amortization	887	471	128
Noncash lease expense	226	—	—
Accretion of purchase discounts and amortization of premiums on investment securities, net	(1,229)	(433)	—
Other	(4)	—	—
Increase (decrease) in cash resulting from changes in:			
Prepaid expenses and other current assets	(2,221)	(1,802)	(783)
Accounts payable and accrued expenses	696	7,361	47
Operating lease liability	(608)	—	—
Deferred rent	—	(261)	15
Net cash used in operating activities	(46,381)	(19,459)	(9,479)
Investing activities:			
Purchases of investment securities	(108,136)	(118,399)	—
Maturities of investment securities	150,295	—	—
Purchases of property and equipment	(492)	(1,059)	(304)
Net cash provided by (used in) investing activities	41,667	(119,458)	(304)
Financing activities:			
Proceeds from issuance of convertible preferred stock, net	—	63,275	11,969
Proceeds from issuance of common stock, net	—	106,472	—
Proceeds from exercise of stock options	126	451	66
Repurchase of unvested shares	(59)	—	—
Repayments of borrowings under long-term debt	—	—	(212)
Net cash provided by financing activities	67	170,198	11,823
Net change in cash, cash equivalents and restricted cash	(4,647)	31,281	2,040
Cash, cash equivalents and restricted cash - beginning of period	45,473	14,192	12,152
Cash, cash equivalents and restricted cash - end of period	$ 40,826	$ 45,473	$ 14,192
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ —	$ —	$ 8
Non-cash financing activity:			
Purchase of shares pursuant to Stock Purchase Plan	$ 735	$ 282	$ —
Change in unvested stock liability	$ 94	$ 21	$ 2
Amounts accrued for purchases of property and equipment	$ 112	$ 42	$ —
Tenant improvement allowance	$ —	$ 3,304	$ —

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.

On July 6, 2018, the Company effected a 1-for-3.29 reverse stock split of its common stock. The par value and the authorized shares of the common stock were not adjusted as a result of the reverse stock split. The reverse stock split resulted in an adjustment to the conversion prices of the Company's Series A and B preferred stock to reflect a proportional decrease in the number of shares of common stock to be issued upon conversion. The accompanying consolidated financial statements and notes to the consolidated financial statements give retroactive effect to the reverse stock split for all periods presented.

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 consolidated statements of operations 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 and Going Concern

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.

As of December 31, 2019, the Company had $118.4 million in unrestricted cash, cash equivalents and investment securities. The Company believes it has sufficient cash to meet its funding requirements for at least the next 12 months. However, the Company has experienced net losses and negative cash flows from operating activities since its inception and has an accumulated deficit of $93.8 million as of December 31, 2019. 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.

On August 13, 2019 the Company 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 having an aggregate offering price of up to $75.0 million through the Sales Agents (the "ATM Offering").

On August 13, 2019, the Company also filed a registration statement on Form S-3 (the "Shelf Registration Statement"), covering the offering of up to $300.0 million of common stock, preferred stock, debt securities, warrants and units. The Shelf Registration Statement included a prospectus covering the offering, issuance and sale of up to $75.0 million of Company

common stock from time to time through the ATM Offering. The Registration Statement became effective on August 29, 2019. The shares to be sold under the Sales Agreement may be issued and sold pursuant to the Shelf Registration Statement.

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 accrued amounts receivable under the Australian research and development tax incentive program, accrued expenses and associated research and development expense, the assumptions underlying the determination of the estimated incremental borrowing rate for the determination of the Company's operating lease right-of-use asset, and the assumptions underlying the determination of the fair value of equity awards for purposes of determining stock-based compensation. Although these estimates are based on the Company's knowledge of current events and actions it may undertake in the future, actual results may ultimately materially differ from these estimates and assumptions.

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.

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.

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 lease 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 included in earnings and are derived using the specific identification method for determining the cost of securities sold. The Company has not realized any significant gains or losses on sales of available-for-sale investment securities during any of the periods presented. As all the Company's investment holdings are in the form of debt securities, unrealized gains and losses that are determined to be temporary in nature are reported as a component of accumulated other comprehensive income. 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 investment income, as are the amortization of purchase premiums and accretion of purchase discounts on investment securities.

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. Beginning January 1, 2019, leases with a term longer than 12 months that are determined to be operating leases are included in operating lease assets, accrued expenses and other current liabilities and noncurrent operating lease liabilities in the consolidated balance sheets based on the present value of the minimum lease payments called for under the arrangement. Lease expense for minimum lease payments is recognized on a straight-line basis over the lease term.

Property and Equipment, Net

Property and equipment, which consist of lab equipment, and computer, software and office equipment, are stated at cost and depreciated on a straight-line basis over the estimated useful life of the related assets (generally three to five years). Leasehold improvements are stated at cost and amortized on a straight-line basis over the lesser of the remaining lease term of the related lease or the estimated useful life of the leasehold improvements.

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

Long-lived assets consist of property and equipment. An impairment loss is recorded if and when events and circumstances indicate that assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amount of those assets. The Company has not recognized any impairment losses in any of the periods presented in these consolidated financial statements.

Deferred Rent

The Company's facility lease includes incentives in the form of rent abatements and leasehold improvement allowances, as well as fixed annual rent escalations. The Company recognizes the aggregate rental expense, after considering incentives and stipulated rent escalations, on a straight-line basis over the lease term. Prior to January 1, 2019, the difference between rent expense and amounts paid under the lease was recorded as deferred rent in the accompanying consolidated balance sheets.

Grant Revenue Recognition

The Company's grant revenues are derived from Small Business Innovation Research Grants ("SBIR Grants") from the National Institutes of Health. The Company recognizes SBIR Grant revenue 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. Earnings in excess of billings are included as a component of prepaid expenses and other current assets.

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. Costs incurred under contracts with contract research organizations ("CROs") that conduct and manage the Company's clinical trials are also included in research and development 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.

Accrued research and development expenses totaled $2.8 million and $3.6 million as of December 31, 2019 and 2018, respectively, and are a component of accounts payable and accrued expenses in the Consolidated Balance Sheets.

Australian Tax Incentive

CAPL is eligible to obtain a cash refund from the Australian Taxation Office for eligible research and development 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 $1.0 million, $1.2 million and $0.5 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Stock-Based Compensation

Stock-based compensation expense represents the estimated grant date fair value of the Company's equity awards, consisting of stock options 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 equity awards using the Black-Scholes option pricing model on the date of grant and recognizes forfeitures as they occur. 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, 2019.

Comprehensive Loss

Comprehensive loss is comprised of the Company's net loss and the unrealized gains on the Company's investment securities for all periods presented.

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 and if-converted methods. Dilutive common stock equivalents are comprised

of convertible preferred stock, 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 would be antidilutive.

Recently Adopted Accounting Pronouncements

ASU 2016-02

In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2016-02, "Leases (Topic 842)" ("ASU 2016-02") which requires lessees to recognize leases on the balance sheet and disclose key information about leasing arrangements. ASU 2016-02 establishes a right-of-use ("ROU") model that requires a lessee to recognize a ROU asset and lease liability on the balance sheet for all leases with a term longer than 12 months. ASU 2016-02 also requires disclosures to meet the objective of enabling users of financial statements to assess the amount, timing, and uncertainty of cash flows arising from leases. On January 1, 2019, the Company adopted ASU 2016-02, and the related ASUs, using the modified retrospective transition method. Under this transition method, the Company recognized and measured leases that existed at the adoption date in the consolidated balance sheet as of January 1, 2019.

ROU assets represent the right to use an underlying asset for the lease term and lease liabilities represent the obligation to make lease payments arising from the lease. Operating lease ROU assets and operating lease liabilities are recognized at the commencement date based on the present value of lease payments over the lease term, discounted at the rate implicit in the lease. If the rate implicit in the lease cannot be determined, Topic 842 requires the use of the rate of interest that a lessee would have to pay to borrow on a collateralized basis over a similar term for a similar amount to the lease payments in a similar economic environment. The operating lease ROU asset is also adjusted for any prepaid or accrued lease payments and any lease incentives received. Operating lease terms may include options to extend or terminate the lease when it is reasonably certain that these options will be exercised. Further, the Company has elected to recognize short-term lease payments on a straight-line basis over the associated lease term and variable lease payments in the period in which the obligation for those payments is incurred. Short-term and variable lease payments were not material in the first half of 2019.

In connection with the adoption of ASU 2016-02, the Company elected the package of practical expedients requiring no reassessment of whether any expired or existing contracts contain leases, the lease classification of any expired or existing leases, or initial direct costs for any existing leases. The Company also made accounting policy elections not to apply the recognition requirements under ASU 2016-02 to any short-term leases and to account for each separate lease and associated non-lease components as a single lease component for the Company's leases.

Adoption of ASU 2016-02 resulted in recognition of a ROU asset of $2.8 million and an operating lease liability of $6.2 million, related to the lease of office and laboratory space; and the derecognition of deferred rent of $3.4 million for certain lease incentives received previously. Adoption of ASU 2016-02 also resulted in recognition of a deferred tax asset and a corresponding deferred tax liability) of $0.7 million. The comparative prior period information continues to be reported under the accounting standards in effect during those periods.

ASU 2018-07

In June 2018, the FASB issued ASU 2018-07, "Compensation-Stock Compensation (Topic 718): *Improvements to Nonemployee Share-Based Payment Accounting*", which expands the scope of Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees and applies to all share-based payment transactions in which a grantor acquires goods or services to be used or consumed in a grantor's own operations by issuing share-based payment awards. This ASU was adopted by the Company on January 1, 2019 using the modified retrospective transition method with no impact on the consolidated financial statements. As a result of adopting this ASU, the estimated fair values of awards issued to non-employees are determined at issuance and are no longer subject to revaluation over their vesting terms.

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 is currently evaluating the impact of the pending adoption of this new standard on its consolidated financial statements.

ASU 2018-13

In August 2018, the FASB issued ASU 2018-13, "Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement," which improves the effectiveness of the disclosures required under ASC 820, "*Fair Value Measurements and Disclosures*" and modifies the disclosure requirements on fair value measurements, including the consideration of costs and benefits. The new standard is effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years, and early adoption is permitted. The Company is currently evaluating the impact of the pending adoption of this new standard on its consolidated financial statements.

3. INVESTMENT SECURITIES

Available-for-sale investment securities consisted of the following as of December 31, 2019 and 2018 (*in thousands*):

	As of December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Market Value
Available-for-sale investment securities:				
U.S. government and agency obligations	$ 43,275	$ 94	$ (1)	$ 43,368
Certificates of deposit	5,931	51	—	5,982
Commercial paper	17,645	—	—	17,645
Corporate debt securities	11,067	7	(3)	11,071
Total	$ 77,918	$ 152	$ (4)	$ 78,066

	As of December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Market Value
Available-for-sale investment securities:				
U.S. government and agency obligations	$ 42,193	$ 72	$ (1)	$ 42,264
Certificates of deposit	5,408	—	—	5,408
Commercial paper	47,686	—	—	47,686
Corporate debt securities	23,554	2	(12)	23,544
Total	$ 118,841	$ 74	$ (13)	$ 118,902

All available-for-sale investment securities held at December 31, 2019 and 2018, had maturity dates of less than 24 months.

None of the Company's available-for-sale investment securities were in a material unrealized loss position at December 31, 2019. The Company reviewed its investment holdings as of December 31, 2019 and determined that its unrealized losses were not considered to be other-than-temporary based upon (i) the financial strength of the issuing institution and (ii) the fact that no securities have been in an unrealized loss position for twelve months or more. As such, the Company has not recognized any impairment in its financial statements related to its available-for-sale investment securities.

4. FAIR VALUE MEASUREMENTS

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.

Financial assets measured at fair value on a recurring basis as of December 31, 2019 and 2018 were as follows (*in thousands*):

	As of December 31, 2019			
	Level 1	Level 2	Level 3	Total
Investment securities:				
U.S. government and agency obligations	$ 15,478	$ 27,890	$ —	$ 43,368
Certificates of deposit	—	5,982	—	5,982
Commercial paper	—	17,645	—	17,645
Corporate debt securities	—	11,071	—	11,071
Total assets measured at fair value	$ 15,478	$ 62,588	$ —	$ 78,066

	As of December 31, 2018			
	Level 1	Level 2	Level 3	Total
Investment securities:				
U.S. government and agency obligations	$ 22,275	$ 19,989	$ —	$ 42,264
Certificates of deposit	—	5,408	—	5,408
Commercial paper	—	47,686	—	47,686
Corporate debt securities	—	23,544	—	23,544
Total assets measured at fair value	$ 22,275	$ 96,627	$ —	$ 118,902

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, 2019 and 2018.

5. BALANCE SHEET DETAILS

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

	December 31, 2019	December 31, 2018
Prepaid research and development costs	$ 2,478	$ 8
Australian tax incentive receivable	929	1,016
SBIR grant receivable	225	568
Interest receivable	224	340
Prepaid expenses and other assets	1,091	876
Total	$ 4,947	$ 2,808

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

	December 31, 2019	December 31, 2018
Leasehold improvements	$ 3,494	$ 3,494
Lab equipment	1,468	915
Office equipment	567	523
Computers and software	41	41
Property and equipment at cost	5,570	4,973
Less accumulated depreciation and amortization	1,624	741
Total	$ 3,946	$ 4,232

6. OPERATING LEASE

2018 Operating Lease. In February 2018, as amended in March 2018, the Company entered into a non-cancelable operating lease for a new facility in San Diego, California. The 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 lease for an additional five years and has a termination option subject to early termination fees. The 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. Rent expense is being

recognized on a straight-line basis over the term of the lease. The Company's estimated incremental fully collateralized borrowing rate of 8.0% was used in its present value calculation as the facility lease does not have a stated rate and the implicit rate was not readily determinable.

Under the terms of the lease, the Company provided the lessor with an irrevocable letter of credit in the amount of $0.5 million. The lessor is entitled to draw on the letter of credit in the event of any default by the Company under the terms of the lease.

*Future Minimum Payments***.** As of December 31, 2019, future minimum payments under non-cancellable operating leases were as follows (*in thousands*):

Year ending December 31,	Minimum Payments
2020	$ 1,123
2021	1,173
2022	1,208
2023	1,244
2024	1,280
Thereafter	871
Total future minimum lease payments	6,899
Less imputed interest	1,326
Total operating lease liability	5,573
Less operating lease liability, current	724
Operating lease liability, non-current	$ 4,849

Rent expense is recorded on a straight-line basis over the term of the Company's facility lease. Rent expense was $1.0 million, $0.6 million and $0.2 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Cash paid for amounts included in the measurement of lease liabilities for operating cash flow from operating leases was $1.1 million during the year ended December 31, 2019.

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. CONVERTIBLE PREFERRED STOCK

In April and December 2017, pursuant to a Series A preferred stock purchase agreement entered into in October 2015 which called for an initial closing and, upon the achievement of certain specified milestones, subsequent closings, the Company issued an aggregate of 11,505,268 shares of Series A convertible preferred stock for gross proceeds of $12.0 million, net of offering costs of $40,000. In February and March 2018, the Company issued an aggregate of 19,641,200 shares of its Series B convertible preferred stock for gross proceeds of $63.5 million, net of issuance costs incurred in connection with this offering of $0.2 million.

The holders of the convertible preferred stock were entitled to certain customary preferences, such as dividend and liquidation priority in relationship to the common shareholders, and certain anti-dilution protection. The convertible preferred stock was classified outside of stockholders' equity (deficit) because the shares contained certain redemption features that were not solely within the control of the Company. In connection with the Company's initial public offering ("IPO"), the outstanding shares of the Company's Series A and Series B convertible preferred stock automatically converted into 14,712,571 shares of common stock (see Note 9).

9. STOCKHOLDERS' EQUITY

Authorized Shares

In connection with the completion of the Company's IPO on July 20, 2018, the Company amended and restated its certificate of incorporation to authorize 200,000,000 shares of common stock, par value $0.001 per share, and 10,000,000 shares of preferred stock, par value $0.001 per share.

Initial Public Offering

The Company completed its IPO in July 2018 whereby it sold 6,900,000 shares of common stock at a price to the public of $17.00 per share. Proceeds from the IPO were approximately $106.5 million, net of underwriting discounts and commissions and offering costs.

Shares of Common Stock Subject to Repurchase

In October 2015, in connection with the issuance of the Company's Series A convertible preferred stock, certain of the Company's founders entered into stock restriction agreements, whereby 1,914,893 of previously unrestricted shares of common stock became subject to repurchase by the Company upon the stockholder's termination of employment or service to the Company. The Company's repurchase rights lapsed as to 765,957 shares of common stock in October 2015, with the remainder scheduled to lapse at the rate of 23,936 shares monthly thereafter such that the shares of common stock would have been fully vested in October 2019. Under the terms of the stock restriction agreements, the shares of common stock were also subject to accelerated vesting upon certain events, such that all of these restricted shares became fully vested upon the closing of the Company's Series B preferred stock financing in February 2018. The stock restriction agreements resulted in the deemed cancellation and reissuance of shares of common stock and therefore, for accounting purposes, the shares subject to repurchase were not considered to be outstanding until vested. The fair value of these shares as of October 2015 was recognized as compensation expense over the vesting period. For the years ended December 31, 2018 and 2017, the Company recognized stock-based compensation for these awards of $0.4 million and $0.2 million, respectively.

10. EQUITY INCENTIVE PLANS

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, 2019, an aggregate of 2,217,222 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, 2020, an additional 1,214,804 shares became available for future issuance under the 2018 Plan.

2015 Stock Incentive Plan

In February 2015, the Company adopted the Crinetics Pharmaceuticals, Inc. 2015 Stock Incentive Plan (the "2015 Plan"), 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, 2019, 33,048 unvested shares issued under early-exercise provisions were subject to repurchase by the Company. The consolidated balance sheet reflects an unvested stock liability of $49,000 and $202,000 as of December 31, 2019 and 2018, respectively.

2018 Employee Stock Purchase Plan

In July 2018, the Company adopted the 2018 Employee Stock Purchase Plan (the "ESPP"). The ESPP permits participants to purchase common stock through payroll deductions of up to 20% of their eligible compensation. As of December 31, 2019, an aggregate of 423,137 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, 2020, an additional 242,961 shares became available for future issuance under the ESPP.

Stock Option Activity

Activity under the Company's stock option plans during the year ended December 31, 2019 was as follows:

	Options Outstanding	Weighted-Average Exercise Price	Weighted-Average Remaining Term	Aggregate Intrinsic Value (000's)
Balance at December 31, 2018	2,339,157	$ 6.40		
Granted	900,175	$ 23.96		
Exercised	(90,322)	$ 1.40		
Forfeited and expired	(21,619)	$ 17.35		
Balance at December 31, 2019	3,127,391	$ 11.52	8.4	$ 42,777
Exercisable at December 31, 2019	1,236,908	$ 6.96	7.9	$ 22,510

Aggregate intrinsic value is calculated as the difference between the closing price of the Company's common stock at December 31, 2019 and the exercise price of stock options that had strike prices below the closing price.

The total intrinsic value of options exercised during 2019 and 2018 was $2.0 million and $2.4 million, respectively.

Fair Value of Stock Option Awards

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	**2019**	**2018**	**2017**
Expected option term	5.9 years	6.0 years	6.0 years
Expected volatility	78%	70%	71%
Risk free interest rate	2.3%	2.8%	2.1%
Expected dividend yield	—%	—%	—%

	Year ended December 31,		
ESPP	**2019**	**2018**	**2017**
Expected option term	1.8 years	1.1 years	N/A
Expected volatility	65%	66%	N/A
Risk free interest rate	2.2%	2.4%	N/A
Expected dividend yield	—%	—%	N/A

The key assumptions used in determining the fair value of equity awards, and the Company's rationale, were as follows: (i) *Expected option term* - the expected term 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; (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; (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.

The weighted-average fair value of stock options granted to employees during the years ended December 31, 2019, 2018 and 2017 was $16.35, $4.66 and $0.85 per share, respectively. The weighted-average fair value of awards under the ESPP during the years ended December 31, 2019 and 2018 was $10.59 and $8.15 per share, respectively.

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,		
	2019	2018	2017
Included in research and development	$ 3,190	$ 1,100	$ 122
Included in general and administrative	3,104	1,220	149
Total stock-based compensation expense	$ 6,294	$ 2,320	$ 271

Unrecognized stock-based compensation cost related to option awards was $17.7 million as of December 31, 2019, which is expected to be recognized over a remaining weighted-average period of approximately 2.8 years. Unrecognized stock-based compensation cost related to stock purchase rights under the Company's ESPP was $0.4 million as of December 31, 2019, which is expected to be recognized over a remaining weighted-average period of approximately 1.2 years.

11. INCOME TAXES

The Company is subject to taxation in the United States, California 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, 2019, the Company had federal, state, and foreign net operating loss ("NOL") carryforwards of approximately $54.5 million, $61.6 million and $0.4 million, respectively. The federal loss carryforwards generated after 2017 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. State loss carryforwards also begin expiring in 2035, unless previously utilized, while the Company's foreign loss carryforwards do not expire. The Company also has federal and California R&D credit carryforwards totaling $4.0 million and $1.9 million, respectively. The federal credits begin to expire in 2030 unless previously utilized, while the state credits do not expire.

Future utilization of the Company's NOL and R&D credit carryforwards to offset future taxable income may be subject to a substantial annual limitation as a result of ownership changes that may have occurred or 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 R&D credit carryforwards that can be utilized to offset future taxable income and 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. The Company has not completed an analysis regarding the limitation of NOL and R&D credit carryforwards.

The Company's federal income tax returns from 2015 forward, state income tax returns from 2014 forward, and its Australian tax returns beginning in 2017 are subject to examination by tax authorities; however, the Company's tax attribute carryforwards such as NOLs and R&D credits generated in closed years are also subject to examination and remeasurement. No such audits are underway

Deferred tax assets and liabilities

Net deferred tax assets are comprised of the following as of December 31, 2019 and 2018 (*in thousands*):

	December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 15,990	$ 2,664
Capitalized research expenses	4,864	6,355
R&D and other tax credits	4,676	1,788
Lease liability	1,560	—
Accrued expenses and other, net	2,229	2,636
Total deferred tax assets	29,319	13,443
Deferred tax liabilities:		
Right-of use asset	(702)	—
Other deferred tax liabilities	(22)	(866)
Net of deferred tax assets and liabilities	28,595	12,577
Less: valuation allowance	(28,595)	(12,577)
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, 2019, domestic and foreign pre-tax loss were (*in thousands*):

	Year ended December 31,		
	2019	2018	2017
Loss before income taxes - Domestic	$ (48,643)	$ (25,876)	$ (8,141)
Loss before income taxes - Foreign	(1,779)	(1,239)	(1,016)
Loss before income taxes - Consolidated	$ (50,422)	$ (27,115)	$ (9,157)

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, 2019 is as follows (*in thousands*):

	Year ended December 31,		
	2019	2018	2017
Expected income tax benefit at federal statutory rate	$ (10,589)	$ (5,694)	$ (3,113)
State income tax benefit, net of federal benefit	(3,431)	(1,758)	(474)
Tax effect of			
Change in valuation allowance	16,064	7,724	2,112
R&D credit	(2,485)	(1,129)	(525)
Federal rate change	—	(52)	1,602
Australian tax incentive	307	362	176
Other	134	547	222
Provision for income taxes	$ —	$ —	$ —

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

	Year ended December 31,		
	2019	2018	2017
Beginning balance	$ 344	$ 159	$ 68
Increase (decrease) for prior year tax positions	70	—	—
Increase (decrease) for current year tax positions	472	185	91
Ending balance	$ 886	$ 344	$ 159

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.

12. NET LOSS PER SHARE

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,		
	2019	2018	2017
Convertible preferred stock outstanding	—	—	8,743
Common stock options	3,127	2,339	838
Unvested common stock subject to repurchase	33	127	527
Total	3,160	2,466	10,108

13. QUARTERLY DATA (*unaudited*)

The following quarterly financial data, in the opinion of management, reflects all adjustments, consisting of normal recurring adjustments, necessary for a fair presentation of results for the periods presented *(in thousands, except per share amounts):*

	Year Ended December 31, 2019			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Grant revenues	$ 367	$ —	$ 505	$ 321
Research and development expenses	$ 7,255	$ 10,285	$ 11,823	$ 12,143
General and administrative expenses	$ 3,156	$ 3,060	$ 3,911	$ 3,392
Total operating expenses	$ 10,411	$ 13,345	$ 15,734	$ 15,535
Net loss	$ (9,016)	$ (12,427)	$ (14,430)	$ (14,549)
Net loss per share – basic and diluted	$ (0.37)	$ (0.51)	$ (0.60)	$ (0.60)

	Year Ended December 31, 2018			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Grant revenues	$ 442	$ 657	$ 548	$ 781
Research and development expenses	$ 4,720	$ 5,222	$ 6,886	$ 7,651
General and administrative expenses	$ 1,248	$ 1,118	$ 1,732	$ 2,561
Total operating expenses	$ 5,968	$ 6,340	$ 8,618	$ 10,212
Net loss	$ (5,464)	$ (5,568)	$ (7,588)	$ (8,495)
Net loss per share – basic and diluted	$ (2.92)	$ (2.41)	$ (0.38)	$ (0.35)

14. SUBSEQUENT EVENTS

Between January 1, 2020 and March 6, 2020, the Company sold a total of 275,764 shares of common stock pursuant to its ATM Offering for net proceeds of $6.4 million, after deducting commissions.

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	7/20/2018	3.2	
4.1	Specimen Stock Certificate Evidencing the Shares of Common Stock	S-1/A	7/9/2018	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				X
10.1#	Crinetics Pharmaceuticals, Inc. 2015 Stock Incentive Plan, as amended	S-1/A	7/9/2018	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	7/9/2018	10.3	
10.4#	Form of stock option agreement under Crinetics Pharmaceuticals, Inc. 2018 Incentive Award Plan	S-1/A	7/9/2018	10.4	
10.5#	Crinetics Pharmaceuticals, Inc. 2018 Employee Stock Purchase Plan and offering document thereunder	S-1/A	7/9/2018	10.5	
10.6#	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	
10.7#	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	
10.8#	Employment Agreement, effective as of June 15, 2018, by and between Alan Krasner, M.D. and the Registrant	S-1/A	7/9/2018	10.8	
10.9#	Form of Indemnification Agreement for Directors and Officers	S-1/A	7/9/2018	10.9	
10.10#	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	
10.11#	Non-Employee Director Compensation Program	S-1/A	7/9/2018	10.11	
10.12	Sales Agreement, dated August 13, 2019, among the Company, SVB Leerink LLC and Cantor Fitzgerald & Co.	S-3	8/13/2019	1.2	
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

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
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	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				X

# 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**.**

Company Name

Date: March 9, 2020

By: /s/ R. Scott Struthers

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 **R. Scott Struthers, Ph.D.**	President, Chief Executive Officer and Director (principal executive officer)	March 9, 2020
/s/ Marc J.S. Wilson **Marc J.S. Wilson**	Chief Financial Officer (principal financial and accounting officer)	March 9, 2020
/s/ Wendell Wierenga, Ph.D. **Wendell Wierenga, Ph.D.**	Chairman of the Board of Directors	March 9, 2020
/s/ Matthew K. Fust **Matthew K. Fust**	Director	March 9, 2020
/s/ Stephen Kaldor, Ph.D. **Stephen Kaldor, Ph.D.**	Director	March 9, 2020
/s/ Weston Nichols, Ph.D. **Weston Nichols, Ph.D.**	Director	March 9, 2020
/s/ Stephanie Okey **Stephanie Okey**	Director	March 9, 2020

Exhibit 4.3

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

Crinetics Pharmaceuticals, Inc. ("Crinetics," "we," "our" and "us") has one class of securities registered pursuant to Section 12 of the Securities Exchange Act of 1934, as amended: our common stock.

Description of Common Stock

General

The following summary of the terms of our common stock does not purport to be complete and is subject to and qualified in its entirety by reference to our Amended and Restated Certificate of Incorporation (the "certificate of incorporation"), and Amended and Restated Bylaws (the "bylaws"), which are filed as exhibits to this Annual Report on Form 10-K and are incorporated by reference herein. We encourage you to read our certificate of incorporation and our bylaws for additional information.

Under our certificate of incorporation, the total number of shares of all classes of stock that we have authority to issue is 210,000,000, consisting of 200,000,000 shares of common stock, par value $0.001 per share and 10,000,000 shares of preferred stock, par value $0.001 per share.

Common Stock

Voting Rights

The holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders, including the election of directors, and do not have cumulative voting rights. Accordingly, the holders of a majority of the outstanding shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they so choose, other than any directors that holders of any preferred stock we may issue may be entitled to elect. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our certificate of incorporation and bylaws also provide that our directors may be removed only for cause and only by the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon. In addition, the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon is required to amend or repeal, or to adopt any provision inconsistent with, several of the provisions of our certificate of incorporation.

Dividends

Subject to preferences that may be applicable to any then outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, the holders of common stock will be entitled to share ratably in the assets legally available for distribution to stockholders after the payment of or provision for all of our debts and other liabilities, subject to the prior rights of any preferred stock then outstanding.

Rights and Preferences

Holders of common stock have no preemptive or conversion rights or other subscription rights and there are no redemption or sinking funds provisions applicable to the common stock.

The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Fully Paid and Nonassessable

All outstanding shares of common stock are duly authorized, validly issued, fully paid and nonassessable.

Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws

Some provisions of Delaware law, our certificate of incorporation and our bylaws contain provisions that could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of the increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Undesignated Preferred Stock

The ability of our board of directors, without action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with voting or other rights or preferences as designated by our board of directors could impede the success of any attempt to change control of us. These and other provisions may have the effect of deferring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings

Our bylaws provide that a special meeting of stockholders may be called only by our chairman of the board of directors, chief executive officer or president, or by a resolution adopted by a majority of our board of directors.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our bylaws establish advance notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

Elimination of Stockholder Action by Written Consent

Our certificate of incorporation and bylaws eliminate the right of stockholders to act by written consent without a meeting.

Staggered Board of Directors

Our board of directors is divided into three classes. The directors in each class will serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Removal of Directors

Our certificate of incorporation provides that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two thirds of the total voting power of all of our outstanding voting stock then entitled to vote in the election of directors.

Stockholders Not Entitled to Cumulative Voting

Our certificate of incorporation does not permit stockholders to cumulate their votes in the election of directors. Accordingly, the holders of a majority of the outstanding shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they choose, other than any directors that holders of our preferred stock may be entitled to elect.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the Delaware General Corporation Law. This statute regulating corporate takeovers prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for three years following the date that the stockholder became an interested stockholder, unless:

- prior to the date of the transaction, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or subsequent to the date of the transaction, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 662/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as an entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by such entity or person.

Choice of Forum

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative form, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders, creditors or other constituents; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. 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. To the extent that any such claims may be based upon federal law claims, Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. Our certificate of incorporation also provides that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

Amendment of Charter Provisions

The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue preferred stock, would require approval by holders of at least two thirds of the total voting power of all of our outstanding voting stock.

The provisions of Delaware law, our certificate of incorporation and our bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or

rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in the composition of our board of directors and management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Listing

Our common stock is listed for trading on the Nasdaq Global Select Market under the symbol “CRNX.”

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

Crinetics Pharmaceuticals, Inc.
San Diego, California

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-233246) and Form S-8 (No. 333-226234) of Crinetics Pharmaceuticals, Inc., of our report dated March 9, 2020, relating to the consolidated financial statements, which appears in this Form 10-K.

/s/BDO USA, LLP

San Diego, California
March 9, 2020

Exhibit 31.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, R. Scott Struthers, Ph.D., certify that:

1. I have reviewed this annual report on Form 10-K of Crinetics Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 9, 2020

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

Exhibit 31.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Marc J.S. Wilson, certify that:

1. I have reviewed this annual report on Form 10-K of Crinetics Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 9, 2020

/s/ Marc J.S. Wilson
Marc J.S. Wilson
Chief Financial Officer

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER

Pursuant to 18 U.S.C. § 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, the undersigned officer of Crinetics Pharmaceuticals, Inc. (the "Company") hereby certifies, to his knowledge, that:

(i) the accompanying Annual Report on Form 10-K of the Company for the fiscal year ended December 31, 2019 (the "Report") fully complies with the requirements of Section 13(a) or Section 15(d), as applicable, of the Securities Exchange Act of 1934, as amended; and

(ii) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

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

Date: March 9, 2020

The foregoing certification is being furnished solely pursuant to 18 U.S.C. Section 1350 and is not being filed as part of the Report or as a separate disclosure document.

Exhibit 32.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER

Pursuant to 18 U.S.C. § 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, the undersigned officer of Crinetics Pharmaceuticals, Inc. (the "Company") hereby certifies, to his knowledge, that:

(i) the accompanying Annual Report on Form 10-K of the Company for the fiscal year ended December 31, 2019 (the "Report") fully complies with the requirements of Section 13(a) or Section 15(d), as applicable, of the Securities Exchange Act of 1934, as amended; and

(ii) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Marc J.S. Wilson

Marc J.S. Wilson
Chief Financial Officer

Date: March 9, 2020

The foregoing certification is being furnished solely pursuant to 18 U.S.C. Section 1350 and is not being filed as part of the Report or as a separate disclosure document.