UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 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, 2020

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: 001-38958

Karuna Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**27-0605902**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
33 Arch Street, Suite 3110 Boston, Massachusetts	**02110**
(Address of principal executive offices)	**(Zip Code)**

(857) 449-2244

(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol(s)	Name of exchange on which registered
Common Stock, $0.0001 Par Value	**KRTX**	**The Nasdaq Global 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 Section 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 the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

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

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

The aggregate market value of the registrant's common stock, $0.0001 par value per share, held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 30, 2020, was $2,231.0 million. For purposes of foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

As of February 15, 2021, there were 27,018,734 shares of the registrant's Common Stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement for its 2021 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2020, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Karuna Therapeutics, Inc.
Index

		Page
	PART I	
Item 1.	Business	5
Item 1A.	Risk Factors	45
Item 2.	Properties	100
Item 3.	Legal Proceedings	100
	PART II	
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	101
Item 6.	Selected Financial Data	101
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	102
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	117
Item 8.	Consolidated Financial Statements and Supplementary Data	117
Item 9A.	Controls and Procedures	150
	PART III	
Item 10.	Directors, Executive Officers and Corporate Governance	152
Item 11.	Executive Compensation	152
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	152
Item 13.	Certain Relationships and Related Transactions, and Director Independence	152
Item 14.	Principal Accounting Fees and Services	152
	PART IV	
Item 15.	Exhibits, Financial Statement Schedules	153
Signatures		156

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K of Karuna Therapeutics, Inc. contains or incorporates statements that constitute forward-looking statements within the meaning of the federal securities laws. Any express or implied statements that do not relate to historical or current facts or matters are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “may,” “will,” “could,” “should,” “expects,” “intends,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “projects,” “seeks,” “endeavor,” “potential,” “continue” or the negative of these terms or other comparable terminology.

These forward-looking statements include, among other things, statements about:

- the timing, progress and results of preclinical studies and clinical trials for KarXT in our current indications and other product candidates we may develop, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work and the period during which the results of the trials will become available;
- our research and development plans, including our plans to explore the therapeutic potential of KarXT in additional indications;
- our plans to develop and commercialize KarXT and other product candidates;
- the timing of and our ability to obtain and maintain marketing approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any product candidates for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional product candidates with significant commercial potential;
- our plans to enter into collaborations for the development and commercialization of product candidates;
- the potential benefits of any future collaboration;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to raise additional capital in sufficient amounts or on terms acceptable to us;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- developments relating to our competitors and our industry; and
- the impact of government laws and regulations.

Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. You are urged to carefully review the disclosures we make concerning these risks and other factors that may affect our business and operating results under “Item 1A. Risk Factors” in this Annual Report on Form 10-K, as well as our other reports filed with the Securities and Exchange Commission. Any public statements or disclosures by us following this Annual Report on Form 10-K that modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this document. The Company does not intend, and undertakes no obligation, to update any forward-looking information to reflect events or circumstances after the date of this document or to reflect the occurrence of unanticipated events, unless required by law to do so.

Summary Risk Factors

The principal risks we face are as follows:

- We are a clinical-stage biopharmaceutical company and we have incurred significant losses since our inception. We anticipate that we will continue to incur significant losses for the foreseeable future.
- Our business substantially depends upon the successful development of KarXT. If we are unable to obtain regulatory approval for or successfully commercialize KarXT, our business may be materially harmed.
- The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time-consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.
- The results of early-stage clinical trials and preclinical studies may not be predictive of future results. Initial data in our clinical trials may not be indicative of results obtained when these trials are completed or in later stage trials.
- Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if obtained.
- We may seek to establish collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.
- Our commercial success depends on our ability to protect our intellectual property and proprietary technology.
- If we fail to comply with our obligations in our current and future intellectual property licenses with third parties, we could lose rights that are important to our business.

PART I

Except where the context otherwise requires or where otherwise indicated, the terms "Karuna," "we," "us," "our," "our company," "the company," and "our business" refer to Karuna Therapeutics, Inc. and its consolidated subsidiary.

ITEM 1. BUSINESS

Overview

We are an innovative clinical-stage biopharmaceutical company driven to create and deliver transformative medicines for people living with psychiatric and neurological conditions. Our pipeline is built on the broad therapeutic potential of our lead product candidate, KarXT, an oral modulator of muscarinic receptors that are located both in the central nervous system, or CNS, and various peripheral tissues. KarXT is our proprietary product candidate that combines xanomeline, a novel muscarinic agonist, with trospium, an approved muscarinic antagonist, to preferentially stimulate muscarinic receptors in the CNS. In November 2019, we completed a Phase 2 clinical trial of KarXT for the treatment of acute psychosis in patients with schizophrenia, EMERGENT-1, in which KarXT met the trial's primary endpoint and was observed to be well tolerated. In December 2020, we initiated EMERGENT-2, the first Phase 3 trial in the EMERGENT program.

Psychosis is a prominent and debilitating symptom that occurs in many neuropsychiatric disorders, including schizophrenia, dementia, bipolar disorder, major depressive disorder and inflammatory neurological diseases, such as multiple sclerosis. Schizophrenia is a chronic disabling disorder that is typically diagnosed in the late teenage years or early adulthood and is characterized by recurring episodes of psychosis requiring long-term treatment with antipsychotic drugs in most patients. The World Health Organization ranks psychosis as the third-most disabling medical condition in the world. In 2017, an estimated 2.7 million Americans, or approximately 0.5% to 1.0% of the United States population, had schizophrenia. Patients with schizophrenia experience psychotic symptoms, also known as positive symptoms, such as hallucinations and delusions. As a result of the disease, patients with schizophrenia also experience negative symptoms, such as amotivation, flat affect and social withdrawal as well as cognitive impairment.

Dementia will affect an estimated 8.4 million people in the United States in 2020, of which approximately 40% are diagnosed with the disease. Dementia includes subtypes of patients suffering from Alzheimer's disease, dementia with Lewy Body, vascular dementia, frontotemporal dementia and Parkinson's disease dementia. Alzheimer's disease, or AD, is the most prevalent cause of dementia, accounting for an estimated 60% to 80% of all cases. The prevalence of psychosis in diagnosed dementia patients varies by dementia subtypes between 10% and 75% and in total an estimated 1.2 million dementia patients exhibit psychiatric symptoms, including up to 50% of patients with AD in the United States, which often leads to institutional care in a hospital or nursing home. Patients with dementia-related psychosis, or DRP, share many characteristics and often exhibit similar psychiatric symptoms irrespective of their underlying neurodegenerative disease.

Worldwide sales of antipsychotic drugs exceeded $11 billion in 2019 and are expected to exceed $20 billion by 2026, despite a highly generic market. Several branded market-leading antipsychotic medicines have each achieved worldwide annual sales in excess of $5 billion. Despite the large number of antipsychotic drugs developed over the last 20 years, current medicines have undergone only modest innovation relative to first generation drugs developed in the 1950s. In many patients, current antipsychotics are hampered by modest efficacy, significant side effects and safety concerns. At least half of patients fail to adequately respond to antipsychotic drugs. Additionally, in many patients, these treatments are associated with severe side effects including sedation, extrapyramidal side effects, such as motor rigidity, tremors and slurred speech, and significant weight gain resulting in the complications of diabetes, hyperlipidemia, hypertension and cardiovascular disease. The clinical benefit of current antipsychotics is further limited by poor adherence. In a 1,493-patient clinical trial funded by the National Institutes of Health, approximately 75% of patients reported discontinuing their antipsychotic medication within 18 months of starting treatment. Current antipsychotic treatments work primarily by inhibiting D2 dopamine receptors and frequently 5HT-2A serotonin receptors and are often used by physicians to address a wide range of disorders in addition to schizophrenia, including bipolar disorder and psychotic depression, as well as psychosis and agitation in elderly patients with dementia.

Muscarinic receptor agonists emerged in the 1990s as a potential alternative approach for treating psychosis. There are five distinct muscarinic receptors, M1 through M5, which are found in the brain as well as various peripheral tissues. The link between muscarinic receptor stimulation in the CNS, particularly stimulation of M1 and M4 receptors, the reduction of psychotic symptoms and improvement in cognition, has been well studied and is supported by data from preclinical studies and two third-party clinical trials published in peer reviewed journals. However, the successful development of a therapeutic agent targeting muscarinic receptors has been limited by undesirable side effects that are believed to arise primarily as a result of stimulation of muscarinic receptors in peripheral tissues. We believe a therapeutic agent that can preferentially target and stimulate muscarinic receptors in the CNS, but not in peripheral tissues, has the potential to treat psychosis in schizophrenia and DRP, including the associated agitation in patients with DRP. We also believe the preferential stimulation of M1 and M4 muscarinic receptors in the CNS may address the negative symptoms of schizophrenia, such as apathy, reduced social drive and loss of motivation, as well as cognitive deficits in working memory and attention, all of which currently lack any approved treatments. This approach has the potential to produce a differentiated therapy relative to current D2 dopamine and 5HT-2A serotonin receptor-based antipsychotic drugs and to beneficially impact the lives of millions of patients with schizophrenia and other psychotic and cognitive disorders.

We are initially developing our lead product candidate, KarXT, for the treatment of acute psychosis in patients with schizophrenia. KarXT combines xanomeline, a muscarinic receptor agonist that preferentially stimulates M1 and M4 muscarinic receptors, and trospium, an approved muscarinic receptor antagonist that does not measurably cross the blood-brain barrier, confining its effects to peripheral tissues. M1 and M4 muscarinic receptors are the receptor subtypes believed to mediate the antipsychotic and procognitive effects of xanomeline and other muscarinic agonists. Results from preclinical studies and clinical trials conducted by third parties support the hypothesis that xanomeline can reduce psychosis and improve cognition. Like all muscarinic receptor agonists studied to date, however, xanomeline's tolerability has been limited by side effects arising from muscarinic receptor stimulation in peripheral tissues, leading to nausea, vomiting, diarrhea and increased salivation and sweating, collectively referred to as cholinergic adverse events. Trospium is a muscarinic receptor antagonist approved in the United States and Europe for the treatment of overactive bladder that inhibits all five muscarinic receptor subtypes in peripheral tissues. We believe that a combination therapy of xanomeline and trospium has the potential to preferentially stimulate M1 and M4 muscarinic receptors in the brain without stimulating muscarinic receptors in peripheral tissues in order to achieve meaningful therapeutic benefit in patients with psychotic and cognitive disorders.

In November 2019, we announced positive results from our EMERGENT-1 trial, a Phase 2 clinical trial evaluating KarXT for the treatment of acute psychosis in patients with schizophrenia. In this trial, KarXT met the trial's primary endpoint with a statistically significant ($p<0.0001$) and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale, or PANSS, scores over placebo at week 5 (-17.4 KarXT vs. -5.9 placebo). We also observed a statistically significant 3.2 point mean reduction from baseline in the PANSS-positive subscale (-5.6 KarXT v. -2.4 placebo) and a statistically significant 2.3 point mean reduction from baseline in the PANSS-negative subscale (-3.2 KarXT v. -0.9 placebo) at week five ($p<0.0001$ and $p<0.001$, respectively). The total PANSS, PANSS-positive subscale, and the PANSS-negative subscale had statistically significant separation at every assessment throughout the trial. Following the positive results of EMERGENT-1, we had an End-of-Phase 2 meeting with the U.S. Food and Drug Administration, or FDA, in which the FDA confirmed that our completed EMERGENT-1 trial, along with one successful Phase 3 efficacy and safety trial, and additional safety data to meet regulatory requirements, would be acceptable to support a New Drug Application, or NDA, filing. Our EMERGENT program includes EMERGENT-2 and EMERGENT-3, which are five-week in-patient trials evaluating the efficacy and safety of KarXT for the treatment of acute psychosis in adults with schizophrenia. Both trials will share key characteristics of EMERGENT-1, such as duration of treatment, patient population, 1:1 randomization, flexible dose regimen, inclusion/exclusion criteria and primary outcome measure, among other aspects. We commenced EMERGENT-2 in December 2020 and expect to commence EMERGENT-3 in the first half of 2021. Following the five-week inpatient phase in both efficacy trials, patients may enter a 52-week open-label safety and tolerability extension in which all patients will receive treatment with KarXT. We also plan to conduct a separate 52-week open-label trial evaluating the long-term safety of KarXT in adults with schizophrenia who have not been enrolled in the inpatient trials. This

trial is expected to begin the first half of 2021. We expect to use the data from these trials to support regulatory safety requirements for a new drug application, or NDA, with the FDA.

In September we presented the results of an exploratory endpoint analysis evaluating the impact of KarXT on cognition in the EMERGENT-1 trial at the European College of Neuropsychopharmacology Annual Meeting. The analysis demonstrated trends towards improvements in cognition for patients receiving KarXT relative to placebo, with larger benefits seen in patients with greater cognitive impairment at baseline.

We are also developing KarXT as a potential treatment for DRP. In the fourth quarter of 2019, we initiated a Phase 1b dose-ranging clinical trial of KarXT designed to evaluate the safety and tolerability of KarXT in healthy elderly volunteers. We are utilizing a flexible dosing protocol titrated over approximately two to three weeks in order to select the doses and titration protocol for future trials of KarXT in elderly patients with DRP. We have completed data collection of the first two cohorts and based on our evaluation of the data, we anticipate Cohort 3 to be the final cohort in the Phase 1b trial, with preliminary data expected in the second quarter of 2021. Data from the two completed cohorts suggest that a lower dose ratio of trospium to xanomeline, compared to the ratios used in the previous trials in healthy adult volunteers and in adults with schizophrenia, was better tolerated by healthy elderly volunteers. Cholinergic and anticholinergic adverse events, or AEs, seen in Cohorts 1 and 2 were similar to those observed in prior trials of KarXT. Based on data from Cohorts 1 and 2 from the on-going trial, we believe that potentially therapeutic doses of KarXT can be administered to elderly adults using titration and flexible dosing while maintaining a favorable tolerability profile to provide a path to a Phase 2 trial evaluating KarXT in DRP. We have commenced planning for this Phase 2 DRP trial, and we expect to provide further guidance following the completion of Cohort 3 later this year.

We plan to initiate a Phase 2 trial evaluating KarXT for the treatment of psychosis in patients with schizophrenia who have an inadequate response to current standard of care therapies. Given the unique mechanism of action of KarXT in comparison to existing standard of care therapies, we believe there is the potential for greater therapeutic benefit with adjunctive treatment. The trial will evaluate the efficacy and safety of KarXT when dosed in conjunction with background antipsychotic treatment. We plan to initiate this trial following the initiation of all trials within the EMERGENT program.

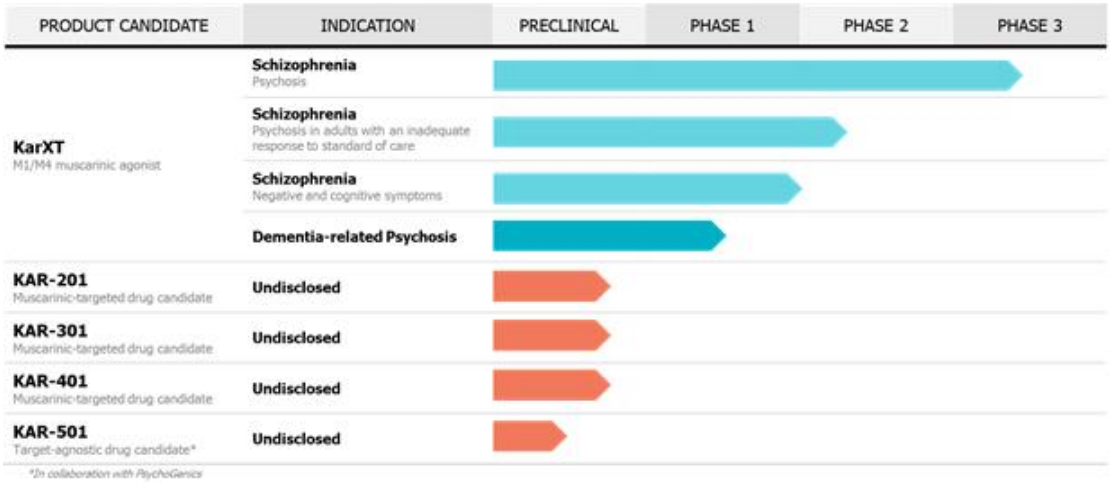
We have assembled a team whose members have extensive expertise in the research, development and commercialization of numerous CNS agents, as well as deep familiarity with the biology of neuropsychiatric disorders, such as schizophrenia and DRP, including the role of muscarinic receptors in potential treatment of these diseases. We plan to leverage this expertise to develop a pipeline of product candidates targeting a broad range of psychiatric and neurological conditions.

Our co-founder and Chief Operating Officer, Andrew Miller, Ph.D., was responsible for identifying, developing and testing the initial hypothesis supporting a combination of xanomeline and trospium. We have since assembled a team of employees and advisors who have expertise and extensive experience in developing psychiatric and neurological drugs, including several former scientists at Eli Lilly and Company, or Eli Lilly, who were actively involved in xanomeline's initial development. Steven Paul, M.D., our Chief Executive Officer, President and Chairman, was formerly the Executive Vice President for Science and Technology and President of the Lilly Research Laboratories at Eli Lilly, where he helped develop the antipsychotic drug Zyprexa and the antidepressant Cymbalta. Dr. Paul was the senior author of the initial publication evaluating xanomeline's effects in treating psychosis and agitation in patients with AD. Stephen Brannan, M.D., our Chief Medical Officer, was previously the Therapeutic Head of Neuroscience at Takeda Pharmaceutical Company Ltd. Alan Breier, M.D., our Chief Clinical Advisor and Chair of our Scientific Advisory Board, was previously Chief Medical Officer at Eli Lilly.

Pipeline

We are advancing a pipeline of therapeutic programs to address the positive, negative and cognitive symptoms associated with schizophrenia and DRP. We are leveraging our expertise and experience to explore

the development of KarXT for additional CNS disorders, as well as advance our other muscarinic-targeted drug candidates and a target-agnostic drug discovery program through our collaboration with PsychoGenics, Inc.



Muscarinic Receptor Biology in the Nervous System

Neurotransmitters are chemical messengers secreted by neurons, or nerve cells, to facilitate information flow and communication with other cells, such as muscle or similar nerve cells, in both the central and peripheral nervous systems. As a result, stimulating or inhibiting neurotransmission can have a profound effect on the overall function of an organism. There are many identified neurotransmitters with a variety of structures and functions. One of the key neurotransmitters in the brain is acetylcholine, for which there are two different receptor classes: ion channel-gated nicotinic receptors, and G protein-coupled muscarinic receptors. Within the muscarinic receptor family, there are five subtypes, M1 through M5, all of which are expressed in the brain and in peripheral tissues.

Muscarinic receptors serve a number of key physiological roles including in cognitive, behavioral, sensory, motor and autonomic processes. Disruption of muscarinic receptor signaling is believed to contribute to psychosis and cognitive impairment in a wide variety of diseases, including schizophrenia and AD. Conversely, third-party preclinical and clinical data suggest that the enhancement of muscarinic receptor signaling leads to improvement in these same symptoms. M1 and M4 muscarinic receptors in particular have been reported to be under-expressed in the brains of patients with schizophrenia. In animal behavioral models, drug candidates that selectively stimulated M1 and M4 muscarinic receptors have demonstrated improvements in psychosis and cognition. Third-party clinical data suggest that stimulation of M1 and M4 muscarinic receptors may similarly be therapeutically beneficial for the treatment of patients with these symptoms. Conversely, inhibition of these receptors has been observed to disrupt memory and cognition, as well as to exacerbate psychosis in patients with schizophrenia.

The stimulation of muscarinic receptors in peripheral tissues can have significant physiological consequences. In peripheral tissues, such as the gastrointestinal and genitourinary tracts, and salivary and sweat glands, M2 and M3 muscarinic receptors are prominently expressed and have specialized functions. In the gastrointestinal tract, muscarinic receptors play a significant role in regulating gastrointestinal motility. Dosing with agonists that stimulate these muscarinic receptors can lead to diarrhea and increased motility, while dosing with muscarinic antagonists can lead to constipation and decreased motility. In the bladder, stimulation or inhibition of muscarinic receptors modulates bladder contraction leading to increases or decreases in urinary frequency, respectively. Similarly, stimulation of muscarinic receptors in salivary glands and sweat glands can lead to increased salivation and sweating, respectively.

Background and Rationale for KarXT

We have designed our lead product candidate, KarXT, to preferentially stimulate M1 and M4 receptors in the brain, without stimulating muscarinic receptors in peripheral tissues outside the CNS. We assessed the potential of over 7,000 possible combinations of muscarinic receptor agonists and antagonists to find an optimized combination that could preferentially stimulate muscarinic receptors in the CNS to improve the symptoms of psychosis, while avoiding stimulation of muscarinic receptors in the peripheral tissues and the associated side effects. As a result of our research, we identified xanomeline and trospium as the most promising pairing for development. Trospium is a potent and effective muscarinic receptor antagonist that does not measurably cross the blood-brain barrier, confining its effects to peripheral tissues. We believe that the combination of xanomeline, a centrally-acting muscarinic agonist, and trospium, a peripherally-acting muscarinic antagonist, will have the therapeutic benefits of xanomeline but with markedly reduced side effects. Based on our clinical data with KarXT, either co-administered or co-formulated, and clinical data of xanomeline published by third parties, we believe that KarXT has potential therapeutic benefit in multiple CNS disorders, including the treatment of the positive, negative and cognitive symptoms of schizophrenia, psychosis and agitation associated with dementia, including AD.

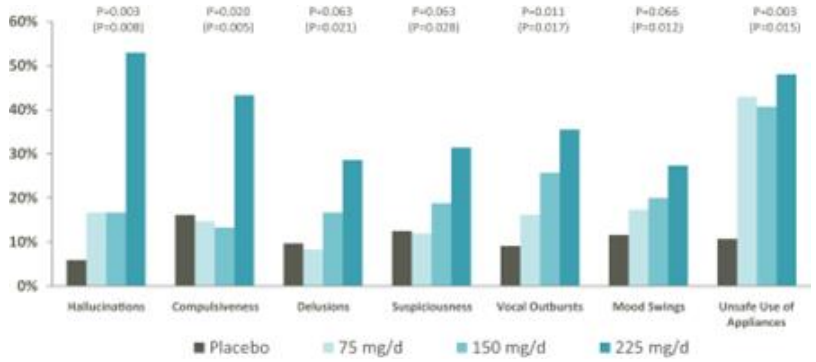
Xanomeline Background

Xanomeline as a treatment for psychosis and related neuropsychiatric disorders has been examined in clinicals trials enrolling over 1,000 subjects or patients conducted by us and third parties, with 68 patients being dosed for at least one year and a maximum treatment duration of almost four years. We believe that the results from these clinical trials, as well as results from numerous preclinical studies, supports the further development of xanomeline, in the form of KarXT, as an antipsychotic and procognitive therapeutic agent.

Xanomeline for the Treatment of Psychotic Symptoms and Agitation in AD

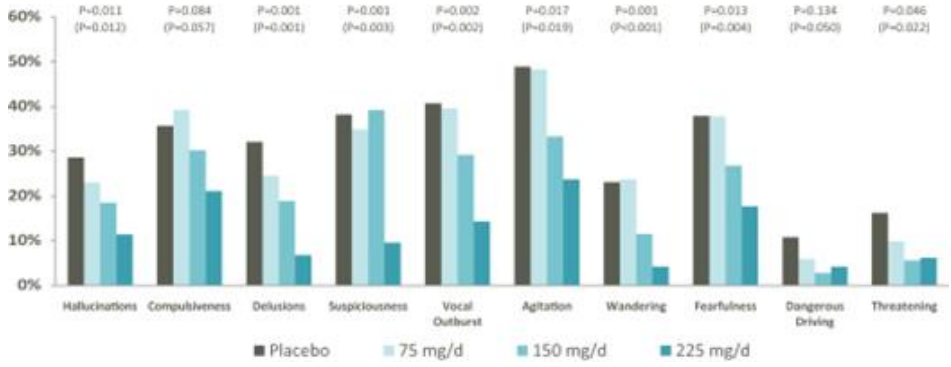
Eli Lilly conducted a 343-patient, randomized, double-blind, placebo-controlled Phase 2 clinical trial of xanomeline in patients with mild to moderate AD, administering up to 225 mg of xanomeline daily (75 mg three times a day, or TID), for 24 weeks. In this clinical trial, 87 patients received placebo, while 85, 83 and 87 patients received 75-150-225 mg of xanomeline, respectively. One patient who entered the trial was assigned to a group but never received study drug or placebo. As shown in the figure below, patients on xanomeline were observed to have dose-dependent decreases in multiple psychotic symptoms and related behaviors, including hallucinations, delusions and agitation, as compared to patients on placebo. For instance, one of the 17 patients (6%) in the placebo arm who presented with hallucinations at baseline had a remission of symptoms while receiving treatment, compared to nine of the 17 patients (53%) in the high-dose xanomeline arm (p=0.003). These responses were seen as early as two to three weeks after commencement of dosing with xanomeline. Xanomeline was also observed to reduce the emergence of psychotic symptoms over the course of the six-month trial in patients who did not have psychotic symptoms at the initiation of the trial. For example, 32% of patients in the placebo arm developed delusions during the trial compared to only 7% in the high-dose xanomeline treatment arm (p=0.001). A dose-response analysis across the 75-150-225 mg xanomeline dose levels reported increasing effects of xanomeline for several symptoms ($P<0.05$), suggesting that exploration of xanomeline doses above 75 mg TID has the potential for additional therapeutic benefits.

Effects of Xanomeline on Psychotic and Related Behavioral Symptoms in AD



p-value represents the comparison of the 225 mg xanomeline arm compared to placebo and, in the case of the p-value in parenthesis, the dose-response analysis.

Effects of Xanomeline on Emergence of Psychosis and Related Behaviors in AD Over Six Months



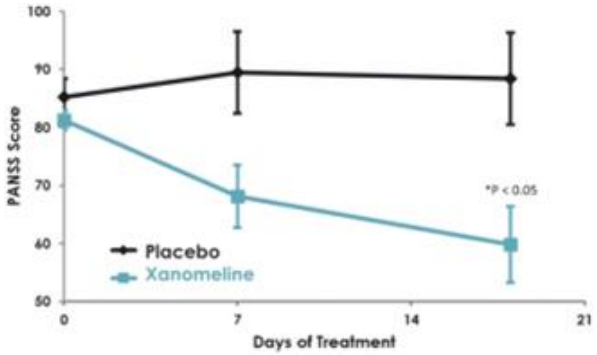
p-value represents the comparison of the 225 mg xanomeline arm compared to placebo and, in the case of the p-value in parenthesis, the dose-response analysis.

In this same trial, cognitive symptoms of patients with AD treated with xanomeline also showed improvements compared to placebo as measured by both the ADAS-Cog and the CIBIC+, suggesting that xanomeline may also improve cognition. The Alzheimer's Disease Assessment Scale-Cognitive Subscale, or ADAS-Cog, is one of the most frequently used tests to measure cognition while the Clinician Interview-Based Impression of Change plus caregiver interview, or CIBIC+, examines disease severity and changes in behavior, cognition and overall function on a scale of 1 to 7, where 1 means markedly improved and 7 means markedly worse. There were high rates of patient discontinuation in the mid-dose (48%) and high-dose (59%) xanomeline cohorts driven in part by side effects, compared to discontinuation rates of 35% and 19% for the placebo and low-dose xanomeline groups, respectively. This high discontinuation rate led to a substantial reduction of statistical power in this trial. Despite this reduction in statistical power, patients in the mid-dose cohort showed a statistically significant benefit on the CIBIC+ as compared to placebo (p=0.02, 4.11 vs. 4.34, respectively). An analysis of patients who completed the trial identified a mean benefit of 2.84 units on the ADAS-Cog for the 225 mg xanomeline arm over placebo (p<0.05), which is similar to the effect seen with donepezil, an approved treatment for the cognitive impairment associated with AD.

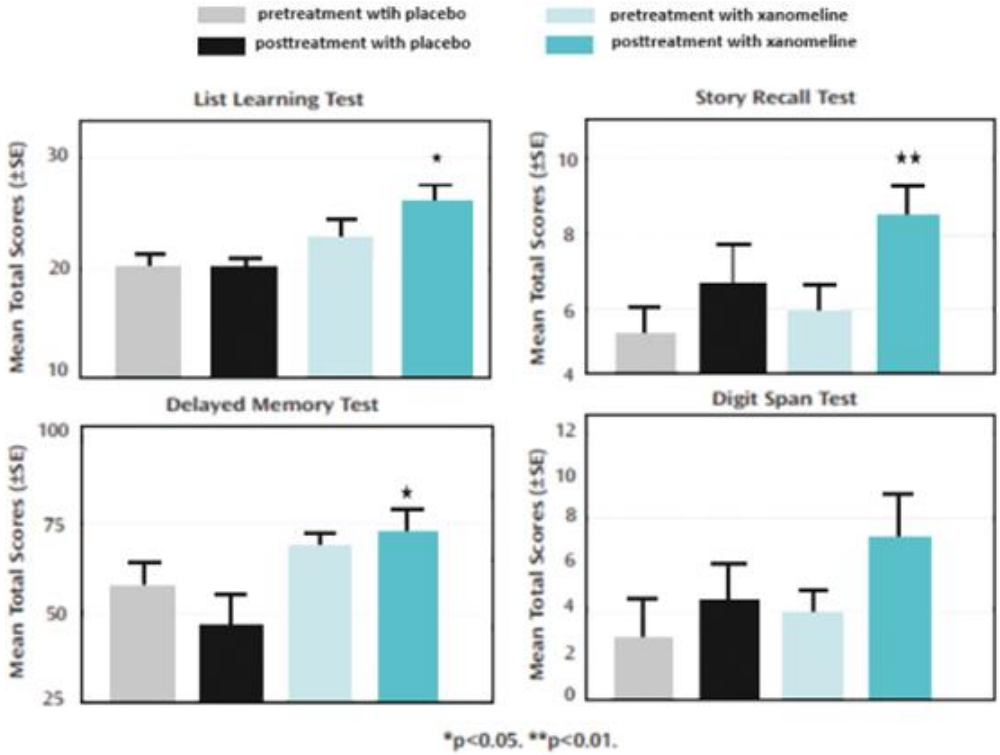
Xanomeline for the Treatment of Psychotic Symptoms in Schizophrenia

A randomized, double-blind, placebo-controlled, Phase 2 trial of xanomeline was conducted in 20 patients with schizophrenia with acute psychosis, as a collaboration between Eli Lilly and the Indiana University School of Medicine. This monotherapy trial used the PANSS as a primary endpoint. The PANSS is a set of measurements used for evaluating symptom severity in patients with schizophrenia and the change in PANSS score has been used as the primary endpoint in many registrational trials of antipsychotic medicines. As depicted in the figure below, a clinically meaningful and statistically significant 24-point PANSS score difference was observed between xanomeline and placebo after 18 days of treatment, which was the pre-specified analysis time point. By comparison, meta-analyses of published clinicals trials of currently approved antipsychotic medicines report an average difference of nine to ten points in PANSS score versus placebo. Historically, changes as small as five points have supported the approval of current antipsychotics. While this xanomeline trial was designed primarily to evaluate changes in positive symptoms, a six-point improvement in negative symptoms, as measured by the PANSS-negative subscale, was also observed in patients treated with xanomeline as compared to placebo. Improvements in cognitive symptoms, including list learning ($p<0.05$), story recall ($p<0.01$), delayed memory ($p<0.05$) and digit span tests were also observed in patients treated with xanomeline as compared to placebo.

Effects of Xanomeline on Psychotic Symptoms in Patients with Schizophrenia



Effects of Xanomeline on Cognition in Patients with Schizophrenia



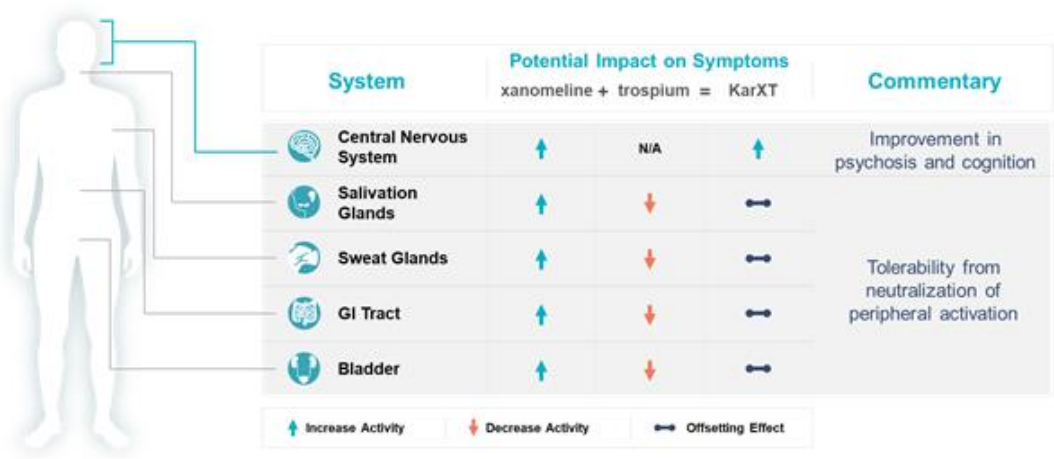
Limitations of Xanomeline

Despite xanomeline's promising therapeutic benefit in treating psychosis and related behavioral symptoms in patients with schizophrenia and AD, its potential has been limited by cholinergic side effects, which are believed to result from the stimulation of muscarinic receptors in peripheral tissues. These side effects led to a 59% dropout rate in the high-dose xanomeline group compared to 35% on placebo in Eli Lilly's six-month AD trial. Syncope, which is a temporary loss of consciousness, was observed in the AD trial (12.6% on high dose xanomeline versus 4.6% on placebo), but not in the schizophrenia trial, in which patients are generally much younger than patients in the AD trial and therefore less prone to syncope. Xanomeline treatment was also associated with transient increases in heart rate and liver function tests, both of which returned to baseline with continued treatment. Electrocardiograms showed no meaningful changes in cardiac conductivity, including QTc interval.

Our KarXT Programs

We specifically designed KarXT, a proprietary combination of xanomeline and trospium, to unlock the therapeutic potential of xanomeline by overcoming its limiting side effects resulting from the stimulation of muscarinic receptors in peripheral tissues. We believe that the results of two third-party, randomized, double-blind, placebo-controlled clinical trials of xanomeline, as well as the results of a wide variety of preclinical studies conducted by third parties, support the further development of xanomeline, in the form of KarXT, as an antipsychotic and procognitive therapeutic agent. We selected trospium to counteract xanomeline's undesirable peripheral side effects for a number of reasons, but importantly because trospium does not measurably cross the blood-brain barrier and therefore would not be expected to negate the therapeutic benefits of xanomeline in the CNS. Trospium is generically available in the United States and European Union for the treatment of overactive bladder and is well-tolerated with limited side effects, that include dry mouth and constipation. Since xanomeline and trospium compete for the same muscarinic receptors in peripheral tissues,

but with opposing effects, we believe their combination has the potential to reduce the cholinergic side effects of xanomeline. We believe that there are no overlaps in the drug metabolism pathways of xanomeline and trospium and therefore we do not anticipate any significant adverse drug-drug interactions with the combination. Our Phase 1 clinical trial data suggests that each of xanomeline and trospium do not affect the other's pharmacokinetics or systemic exposure.



We believe that the novel mechanism of KarXT has the potential to provide meaningfully better outcomes for patients suffering from schizophrenia and other neuropsychiatric conditions without the debilitating side effects of current D2 dopamine receptor-based therapies, including sedation, extrapyramidal side effects, such as motor rigidity, tremors and slurred speech, and significant weight gain resulting in the complications of diabetes, hyperlipidemia, hypertension and cardiovascular disease. We obtained an exclusive license to xanomeline from Eli Lilly along with a large database of preclinical and clinical data generated by Eli Lilly supporting xanomeline's development. Our team of employees and advisors includes several former scientists at Eli Lilly who were actively involved in xanomeline's preclinical and clinical development to help us advance the development of KarXT.

Proof of Concept of KarXT

Phase 1 Clinical Trials

We observed KarXT's ability to ameliorate the side effects of xanomeline in our randomized, double-blind, placebo-controlled, Phase 1 clinical trial in 70 healthy volunteers conducted under our investigational NDA. In this trial, we compared the tolerability profile and pharmacokinetics of xanomeline administered with placebo against KarXT co-administered as xanomeline in combination with trospium. Volunteers in this trial first received 40 mg (20 mg twice a day, or BID) of either trospium or placebo for two days, and then received 225 mg of xanomeline (75 mg TID) in addition to their existing regimen of trospium or placebo for seven days. We selected the 225-mg (75 mg TID) dose for evaluation in our trial due to the results of this dose in Eli Lilly's schizophrenia and AD trials of xanomeline. As depicted in the table below, we observed that the addition of trospium to xanomeline was associated with clinically meaningful reductions in the rate of the most common treatment-emergent cholinergic adverse events, or ChAEs, than reported with xanomeline plus placebo, including nausea, vomiting, diarrhea and excess sweating and salivation. The overall ChAE rate was 64% on xanomeline plus placebo compared to 34% on KarXT (p=0.016). The rate of ChAEs for volunteers receiving KarXT (34%) was similar to the rate observed in volunteers receiving placebo during the lead-in period (32%), suggesting that the tolerability of KarXT was more similar to the placebo lead-in period than to treatment with xanomeline plus placebo.

ChAE Incidence Rates	Xanomeline+ placebo N=33	KarXT N=35	% Reduction in Incidence Rates
Any Cholinergic AE (p=0.016)	**64%**	**34%**	**46%**
Nausea	24%	17%	29%
Vomiting	15%	6%	62%
Diarrhea	21%	6%	73%
Sweating	49%	20%	59%
Salivation	36%	26%	29%

We observed no meaningful differences between the KarXT and xanomeline plus placebo treatment groups in heart rate, blood pressure or any electrocardiogram parameters. Only one volunteer discontinued treatment due to treatment emergent adverse events in the KarXT arm, and this discontinuation was voluntary, not at the discretion of the investigator. Two episodes of syncope were observed on xanomeline plus placebo while none were observed with KarXT. We did not observe syncope in the KarXT arm of this trial (or in any other subject treated with KarXT in any of our trials, representing over 140 patients). Rates of postural dizziness were reduced by approximately 57% in patients treated with KarXT as compared to patients treated with xanomeline plus placebo. Overall, we considered treatment with xanomeline 225 mg combined with trospium 40 mg administered over seven days to be well-tolerated.

Phase 1 Multiple Ascending Dose Clinical Trial

We have also completed a randomized, double-blind, placebo-controlled multiple ascending dose Phase 1 clinical trial of KarXT. This trial evaluated BID dosing of our proprietary KarXT co-formulation containing fixed ratios of xanomeline and trospium, rather than the TID dosing previously used with xanomeline. We designed our Phase 1 clinical trial based on the improved tolerability of KarXT over xanomeline plus placebo observed in our prior Phase 1 clinical trial and the dose-dependent clinical activity observed in the Eli Lilly AD trial of xanomeline. In particular, Eli Lilly observed that the antipsychotic effect of xanomeline improved when the dose was increased from 25 mg to 50 mg to 75 mg, all administered TID, suggesting that the dose response may extend beyond 75 mg TID and that doses of xanomeline higher than 75 mg TID may lead to additional therapeutic benefit. Based on these observations, we set out to (i) test our co-formulation using BID dosing, (ii) explore higher doses of xanomeline and (iii) optimize the ratio of xanomeline and trospium. Healthy volunteers enrolled in this trial received 50 mg of xanomeline plus 20 mg of trospium (50/20 mg) both BID, on days one and two. From days three to seven, volunteers received BID doses of xanomeline and trospium in ratios of either 100/20 mg, 125/40 mg, 150/20 mg or 150/40 mg (xanomeline/trospium) in different dosing cohorts. The trial was designed to randomize up to 24 volunteers in each of the four cohorts, with a 3:1 randomization of KarXT to placebo.

In this trial, administration of KarXT co-formulation provided robust xanomeline and trospium exposures as measured by plasma levels. In particular, KarXT containing xanomeline 100 mg BID provided drug exposures equivalent to, or higher than, 75 mg of xanomeline TID when administered alone. KarXT was also well-tolerated in volunteers at dose levels of 100 mg and 125 mg of xanomeline BID when paired with 20 mg and 40 mg of trospium, respectively.

Eighteen volunteers received KarXT in the 100/20 mg cohort. In this group, 16 volunteers experienced either no ChAEs (n=11; 61%) or mild, transient ChAEs (n=5; 28%). The majority of ChAEs were reported for less than one hour over the seven days of treatment and the longest duration reported was a total of 15 hours over the course of treatment. Two volunteers (11%) experienced transient ChAEs that were rated as moderate, with the longest ChAE lasting a total of approximately 11 hours over the course of treatment. Given the transient and generally mild nature of the ChAEs, we considered the 100/20 mg dose level of KarXT well tolerated. Eighteen volunteers were given the 125/40 mg dose level of KarXT, of which 11 volunteers (61%) reported no ChAEs and seven volunteers (39%) reported mild, transient ChAEs. These mild ChAEs lasted less than three hours over the course of the seven-day treatment period. The increased dose of trospium (40 mg BID) was associated with reports of mild anticholinergic adverse events, including dry mouth, constipation, blurred vision and urinary hesitancy, suggesting a decreased trospium dose level may be more appropriate to pair with 125 mg BID of xanomeline. Xanomeline doses of 150 mg in KarXT led to increased reporting of moderate ChAEs and were therefore less well-tolerated than either the 100 or 125 mg xanomeline doses.

In this Phase 1 clinical trial, we observed that KarXT doses containing either 100 mg or 125 mg of xanomeline administered BID were well-tolerated when paired with trospium. Importantly, the 100 mg BID dose level administered in our co-formulation provided blood exposures equal to or greater than those observed by us and Eli Lilly with 75 mg TID xanomeline, which was observed to have beneficial effects on psychosis and cognition in both schizophrenia and AD. While a minority of patients still experienced ChAEs, these were predominately mild and transient in nature. We believe this tolerability profile has the potential to provide a substantial improvement over current antipsychotic medicines, which are often not tested at therapeutic doses in healthy volunteers due to their poor tolerability. Based on the results of this trial, we identified 100/20 mg and 125/30 mg BID as the doses and ratios of xanomeline to trospium to evaluate in our Phase 2 clinical trial of KarXT for acute psychosis in patients with schizophrenia.

We submitted an Investigational New Drug application to the U.S. Food and Drug Administration, or the FDA, for KarXT for the treatment of schizophrenia, which went into effect in August 2016.

KarXT for the Treatment of Acute Psychosis in Patients with Schizophrenia

Schizophrenia is a chronic, severe and disabling brain disorder. In 2017, an estimated 2.7 million Americans, or approximately 0.5% to 1.0% of the U.S. population, had schizophrenia. Worldwide, it is estimated that schizophrenia affects over 21 million people. People with schizophrenia have a 10 to 15-year reduction in life expectancy compared to the general population, struggle to maintain employment or live independently and are often unable to maintain meaningful interpersonal relationships.

Psychosis is a prominent and debilitating symptom that occurs in schizophrenia. Psychotic symptoms, also known as positive symptoms, include hallucinations and delusions. Patients with schizophrenia also experience negative symptoms, such as apathy, reduced social drive, loss of motivation and lack of social interest. Schizophrenia is also often associated with significant cognitive impairment, which further limits a patient’s ability to be gainfully employed and maintain relationships.

Worldwide sales of antipsychotic drugs exceeded $11 billion in 2015 and are expected to exceed $14 billion by 2025, despite a highly generic market. Several branded market leading antipsychotic medicines have each achieved worldwide annual sales in excess of $5 billion. Despite the large number of antipsychotic drugs developed over the last 20 years, current medicines have undergone only modest innovation relative to first generation drugs developed in the 1950s.

Current antipsychotics have modest efficacy in many patients and significant side effects and safety concerns. At least half of patients fail to adequately respond to current antipsychotic drugs. Additionally, current treatments are often associated with severe side effects, including sedation, extrapyramidal side effects such as motor rigidity, tremors and slurred speech, and significant weight gain resulting in the complications of diabetes, hyperlipidemia, hypertension and cardiovascular disease. The clinical benefit of current antipsychotics is further limited by poor adherence. In a 1,493-patient clinical trial funded by the National Institutes of Health, approximately 75% of patients reported discontinuing their antipsychotic medication within 18 months of starting treatment.

Current antipsychotic treatments work primarily by inhibiting D2 dopamine receptors and are often used by physicians to address a wide range of disorders in addition to schizophrenia, including bipolar disorder and psychotic depression, as well as psychosis and agitation in elderly patients with dementia. These treatments are approved for the treatment of positive symptoms of schizophrenia, such as hallucinations and delusions, but there are no approved therapies for the treatment of negative and cognitive symptoms of schizophrenia. We believe there is a substantial need for a new antipsychotic drug that has an improved efficacy and side effect profile, and for a drug that can treat the negative and cognitive symptoms of the disease.

The regulatory requirements, including clinical trial design and primary endpoints, for approval of antipsychotic drugs for this indication are well understood and defined. Similarly, third-party clinical trial operators and contract research organizations have extensive experience conducting drug trials in schizophrenia. Finally, patients with schizophrenia in clinical trials are generally younger than patients suffering psychosis from other CNS disorders such as DRP, which reduces the risk of comorbidities, and patients with schizophrenia also tend to have higher drug tolerability due to their prior treatment with antipsychotic drugs. We believe that these factors will help us to efficiently progress KarXT in this indication.

Our Phase 2 Clinical Trial for the Treatment of Acute Psychosis

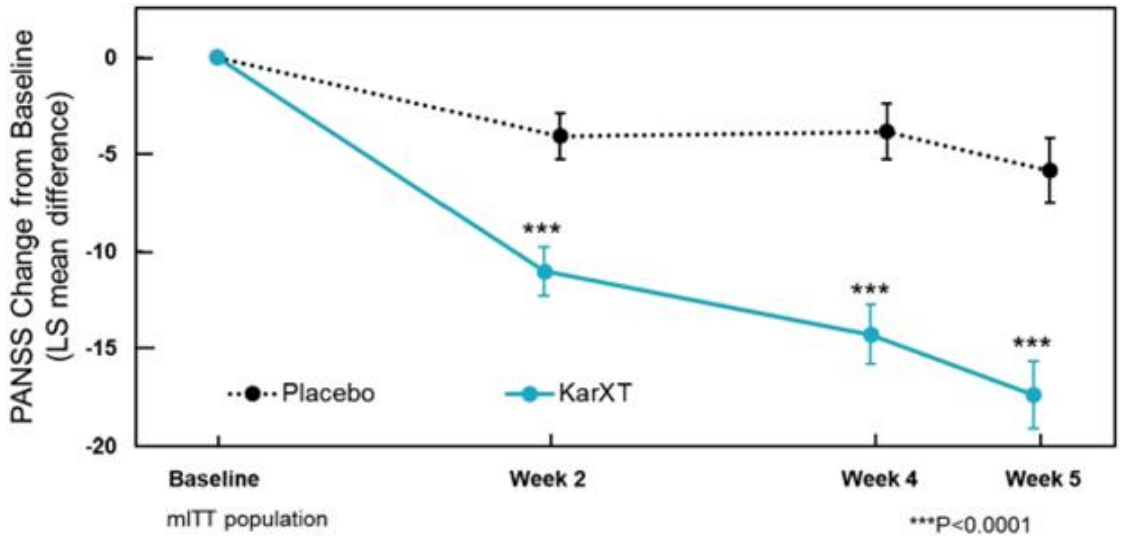
In September 2018, we initiated EMERGENT-1, a multi-site, double-blind, placebo-controlled, five-week, inpatient Phase 2 clinical trial of KarXT in patients with schizophrenia with acute psychosis. We enrolled 182 patients in this trial and patients were randomized 1:1 to receive either KarXT or placebo. Patients were washed out of any existing antipsychotic medications before entering the five-week active treatment or placebo phase. After the wash-out period, patients began with either placebo or KarXT containing 50 mg xanomeline and 20 mg trospium (50/20 mg) BID. Patients receiving KarXT then increased their dose to 100/20 mg BID on day three and then physicians had the option to escalate to 125/30 mg BID starting on day eight if the 100/20 mg BID dose was well-tolerated. The primary endpoint in this trial was the change from baseline in PANSS total scores for KarXT versus placebo treated patients at week five. Our trial had the same fundamental design and primary endpoint as the previous xanomeline trial in psychosis in schizophrenia, which is also the design that has been used in pivotal trials for several currently approved antipsychotic medicines. Additional endpoints of our trial included changes in PANSS Marder Factor score (including the negative symptom factor), a cognitive battery and the clinical global impression (CGI-S).

In November 2019, we announced topline results from our EMERGENT-1 trial, in which KarXT met the trial's primary endpoint with a statistically significant ($p<0.0001$) and clinically meaningful 11.6 point mean reduction in total PANSS scores over placebo at week 5 (-17.4 KarXT vs. -5.9 placebo). We also observed a statistically significant 3.2 point mean reduction from baseline in the PANSS-positive subscale (-5.6 KarXT v. -2.4 placebo) and a statistically significant 2.3 point mean reduction from baseline in the PANSS-negative subscale (-3.2 KarXT v. -0.9 placebo) at week five ($p<0.0001$ and $p<0.001$, respectively). The total PANSS, PANSS-positive subscale, and the PANSS-negative subscale had statistically significant separation at every assessment throughout the trial.

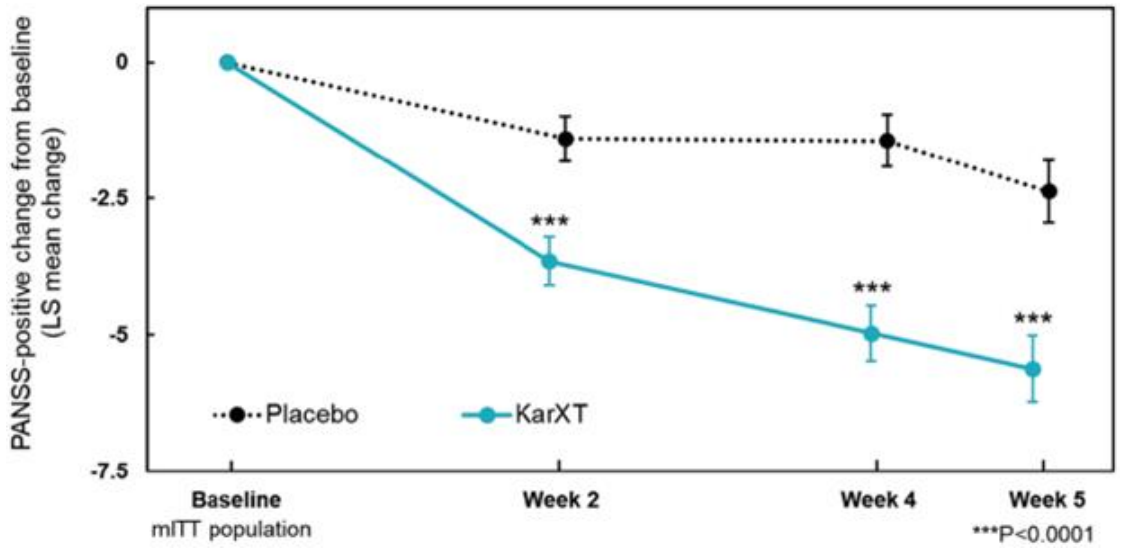
In addition, we analyzed additional pre-specified secondary endpoints, including PANSS-Marder factor score, CGI-S frequency counts and percentage of CGI-S responders, defined as a CGI-S rating of either 1 or 2 at week five. We observed a statistically significant 2.5 point mean reduction from baseline in the PANSS Marder factor score (-3.9 KarXT v. -1.3 placebo) at week five ($p<0.001$). The PANSS Marder factor score had statistically significant separation at every assessment point through the trial. We also observed statistically

significant different CGI-S frequency counts for KarXT compared to placebo at week five (p<0.001). A 4:1 ratio of CGI-S responders (5.6% KarXT v. 1.4% placebo) was also observed, however this result was not statistically significant (p=0.151).

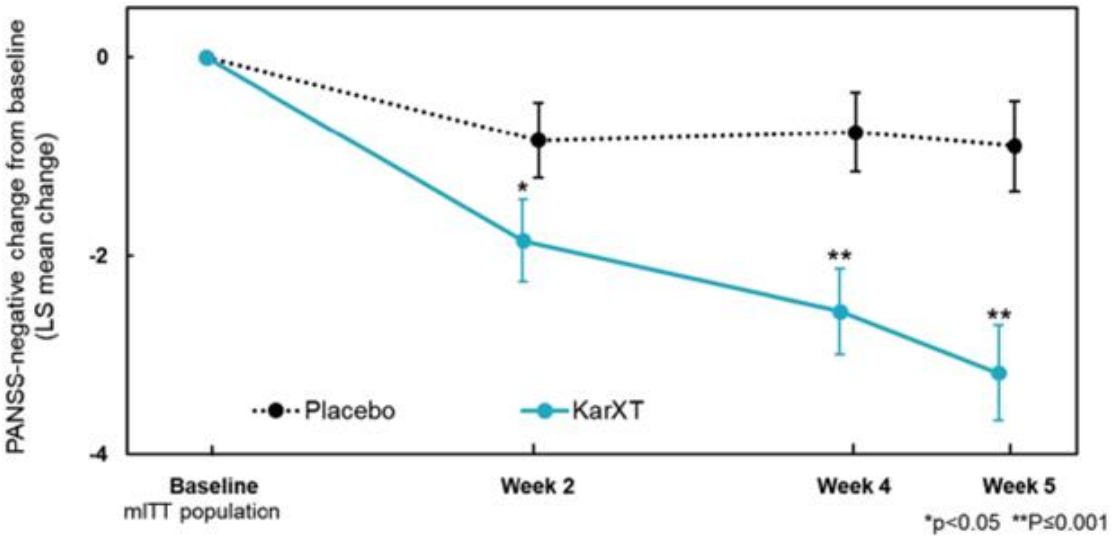
Effect of KarXT on Total PANSS



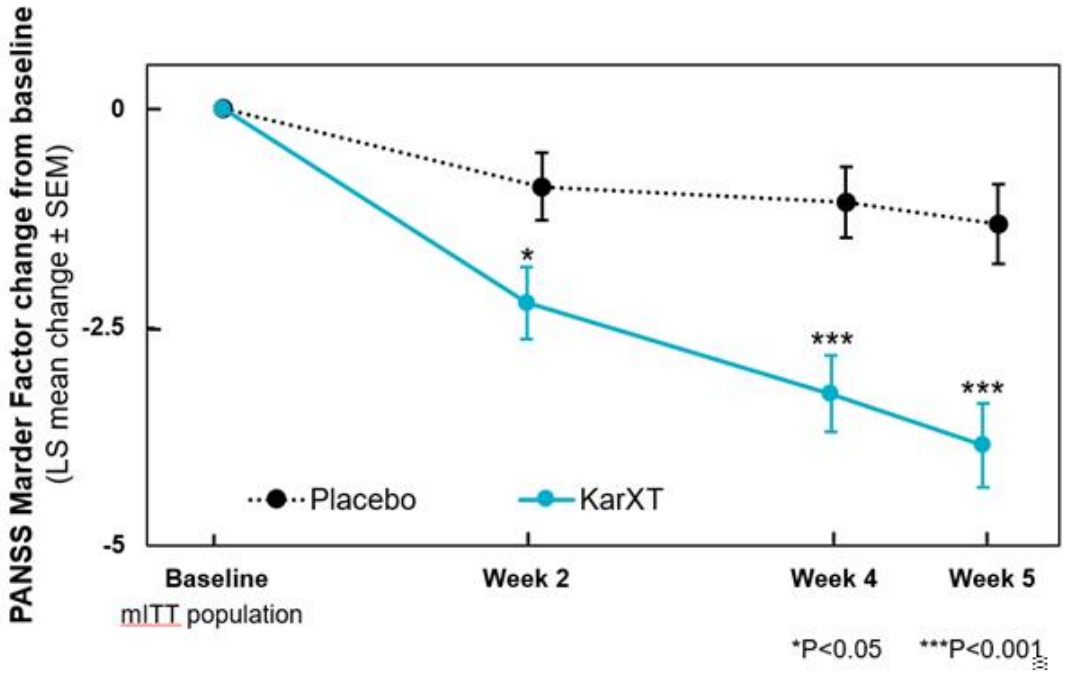
Effect of KarXT on Positive PANSS



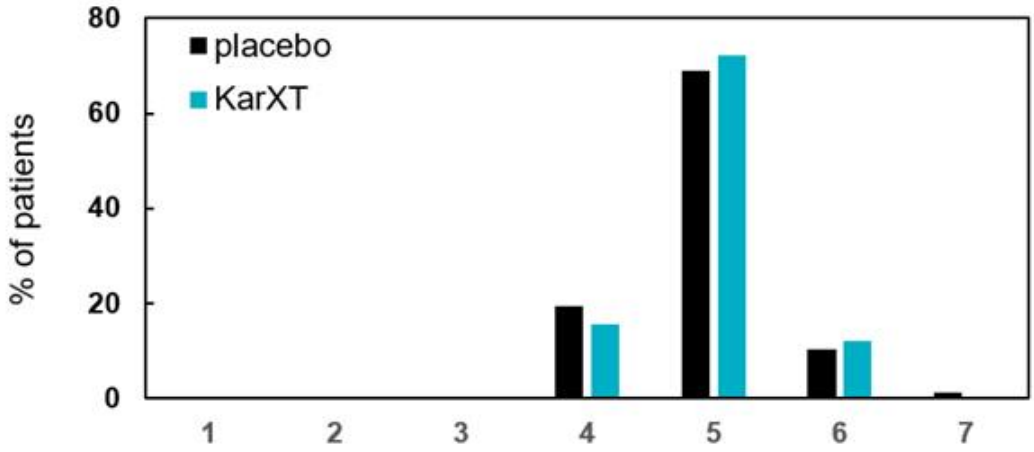
Effect of KarXT on Negative PANSS



Effect of KarXT on PANSS Marder factor

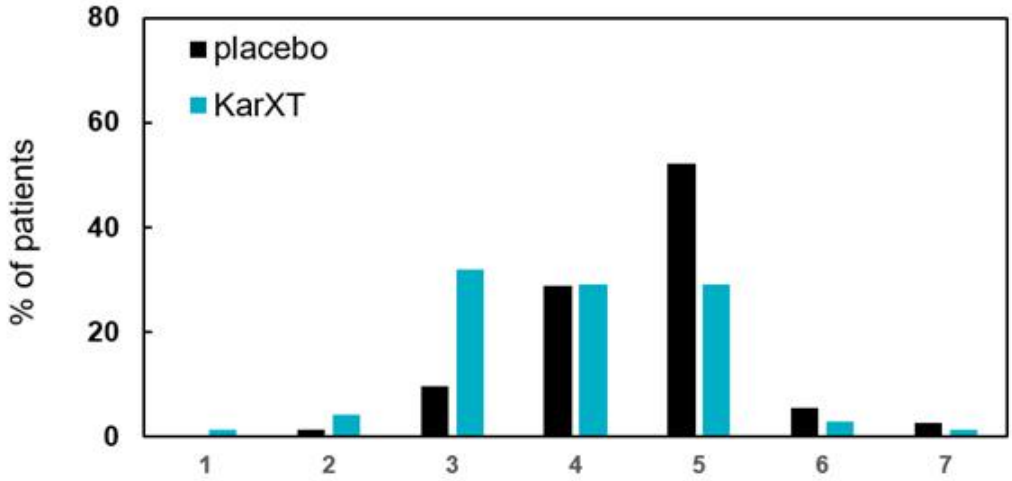


CGI-S distribution at baseline



1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = extremely ill

CGI-S distribution at week 5



1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = extremely ill

KarXT was observed to be well tolerated in this Phase 2 trial. The overall discontinuation rate in the KarXT treatment arm was similar to placebo (20% on KarXT vs. 21% on placebo) and the number of discontinuations due to treatment emergent adverse events was equal in the two arms (n=2 on KarXT and n=2 on placebo). No patients discontinued treatment due to cholinergic adverse events in either arm of the trial. 91% of patients treated with KarXT escalated to the high dose of KarXT as part of the flexible dose design, where the choice to escalate was made by the site physician based on the tolerability of KarXT on an individual patient basis. 97% of placebo patients were dose escalated. There was also the option to de-escalate back to

100/20 mg BID KarXT dose if any tolerability issues emerged, and only 4% of patients were de-escalated in the KarXT arm compared to 1% on placebo. The overall treatment emergent adverse event rate was 54% on KarXT and 43% on placebo. Occurrences of drowsiness, extrapyramidal side effects, such as tremors or slurred speech, or weight gain, which are adverse effects generally associated with current antipsychotic drugs, were similar to placebo. The most common adverse events were constipation, nausea, dry mouth, abdominal discomfort, and vomiting, all of which were mild or moderate in severity and transient in nature. Placebo-adjusted rates of nausea, vomiting and dry mouth all decreased over time during the trial. There was no syncope, and there was no mean change in blood pressure. One patient in the KarXT group discontinued due to elevated gamma-glutamyl transferase. There was a 5.5 beats per minute peak mean placebo adjusted resting heart rate increase in the KarXT group, with a downward trend after week 2. One serious adverse event was observed in the KarXT treatment group, in which a patient discontinued and sought hospital care for worsening psychosis, meeting the regulatory definition of serious adverse event. The clinical trial administrator was not able to rule out that the serious adverse event was drug related, and as such, the serious adverse event was classified as being “possibly-drug related.” All other treatment emergent adverse events were mild or moderate.

Our Ongoing and Planned Clinical Trials for the Treatment of Acute Psychosis in Adults with Schizophrenia

Following the positive results of EMERGENT-1, we had an End-of-Phase 2 meeting with the FDA in which the FDA confirmed that our completed EMERGENT-1 trial, along with one successful Phase 3 efficacy and safety trial, and additional safety data to meet regulatory requirements, would be acceptable to support an NDA filing. As such, we will conduct the following trials as part of our EMERGENT program, which together with additional preclinical, CMC, clinical and other related activities will support our NDA filing for KarXT for the treatment of acute psychosis in adults with schizophrenia:

- EMERGENT-2 is a five-week, inpatient, 1:1 randomized, flexible-dose, double-blind, placebo-controlled trial evaluating the efficacy and safety of KarXT in 246 adults with schizophrenia in the U.S. EMERGENT-2 was initiated in December 2020.
- EMERGENT-3 is a five-week, inpatient, 1:1 randomized, flexible-dose, double-blind, placebo-controlled trial evaluating the efficacy and safety of KarXT in 246 adults with schizophrenia in the U.S. and E.U. We expect EMERGENT-3 to initiate in the first half of 2021.
- EMERGENT-4 is a 52-week, outpatient, open-label extension trial evaluating the long-term safety and tolerability of KarXT in adults with schizophrenia who completed EMERGENT-2 or EMERGENT-3. EMERGENT-4 enrolled its first patient in the first quarter of 2021.
- EMERGENT-5 is a 52-week, outpatient, open-label trial evaluating the long-term safety and tolerability of KarXT in adults with schizophrenia who have not been enrolled in the EMERGENT-2 or EMERGENT-3 trials. We expect to commence EMERGENT-5 in the first half of 2021.

We also plan to initiate a Phase 2 trial evaluating KarXT as an adjunctive therapy with standard of care for the treatment of psychosis in patients with schizophrenia who remain symptomatic on existing therapies. We previously planned to initiate a Phase 1b trial assessing potential Drug-Drug Interactions with a selection of currently marketed antipsychotics in healthy volunteers, but based on multiple considerations, including the evaluation of existing preclinical and clinical data supporting the potential of KarXT to augment traditional antipsychotic drugs, we plan to move forward directly to initiate a Phase 2 trial. The trial will evaluate the efficacy and safety of KarXT when dosed in conjunction with background antipsychotic treatment and its potential to improve symptoms in patients who had not achieved an adequate response on their current antipsychotic treatment. We plan to initiate this trial following the initiation of all trials within the EMERGENT program.

Our Planned Clinical Trials for the Negative and Cognitive Symptoms of Schizophrenia

We plan to utilize the data from our EMERGENT-1 trial to help us guide KarXT’s future development for negative and cognitive symptoms of schizophrenia, for which there are currently no approved treatments.

In September 2020 we presented the results of an exploratory endpoint analysis evaluating the impact of KarXT on cognition in the EMERGENT-1 trial at the European College of Neuropsychopharmacology Annual Meeting. The analysis demonstrated trends towards improvements in cognition for patients receiving KarXT relative to placebo, with larger benefits seen in patients with greater cognitive impairment at baseline. We plan to collect data on the potential benefit of KarXT on negative and cognitive symptoms of schizophrenia as part of the ongoing EMERGENT program and our planned trial to evaluate KarXT in patients who have an inadequate response to current standard of care therapies described below, and will continue to evaluate the timing and design of potential trials specifically directed towards the negative and cognitive symptoms of schizophrenia.

Cognitive performance results

Cognitive Test	Statistic (KarXT vs. placebo)	Value
Composite Score*	p-value	0.11
	Cohen's d	0.24

*Composite score of six cognitive battery tests, including: Detection, Pediatric Groton Maze Learning, Identification, International Shopping List, One-Back Speed, One-Back Accuracy

Composite score analysis stratification by baseline impairment

Statistic (KarXT vs. placebo)	Impairment Median Split		Impairment Tertile Split		
	High	Low	Highest	Middle	Lowest
p-value	**0.03**	0.53	**0.02**	0.52	0.87
Cohen's d	**0.56**	0.13	**0.83**	0.19	0.04

KarXT for the Treatment of Dementia-Related Psychosis

Approximately 8.4 million people in the United States are living with dementia of which approximately 40% are diagnosed with the disease. The prevalence of psychosis in diagnosed dementia patients varies by dementia subtypes between 10% and 75% and in total an estimated 1.2 million dementia patients exhibit psychiatric symptoms. Patients with DRP share many characteristics and often exhibit similar psychiatric symptoms irrespective of their underlying neurodegenerative disease. AD is the most common form of dementia and represents between 60% and 80% of dementia patients. AD is an irreversible, progressive neurodegenerative brain disorder that slowly destroys memory and cognition and, eventually, the ability to carry out even the simplest of tasks. In the large and growing AD population, up to 50% of patients will experience psychosis and related behavioral symptoms at some point during the course of their disease, which often leads to institutional care in a hospital or nursing home. Based on third-party clinical trials with xanomeline and xanomeline's mechanisms of action, we believe KarXT has therapeutic potential to treat DRP. To date, the FDA has not approved any drug to treat the psychotic or behavioral symptoms of DRP. As symptoms progress and become more severe, physicians often resort to off-label use of antipsychotic medications to treat these patients. Current antipsychotic drugs are associated with a number of side effects including potentially irreversible movement disorders, weight gain, metabolic dysfunction and sedation, which can be more problematic in elderly patients with DRP. In addition, antipsychotic drugs all have a "boxed warning" for increased mortality in the elderly and may exacerbate the cognitive impairment associated with DRP. Accordingly, there remains a large unmet medical need in psychosis and the associated behavioral symptoms of patients with DRP.

Our On-Going Phase 1b Healthy Elderly Volunteer Clinical Trial

Based on Eli Lilly's Phase 2 clinical trial of xanomeline in patients with AD, and the improved tolerability profile of KarXT as compared to xanomeline, in December 2019, we initiated a Phase 1b dose-ranging clinical trial to assess the safety and tolerability of KarXT in healthy elderly volunteers. We are utilizing a flexible dosing protocol titrated over approximately two to three weeks in order to select the doses and titration protocol for future trials of KarXT in elderly patients with DRP.

We have completed data collection of the first two cohorts in our ongoing Phase 1b trial in healthy elderly volunteers. Based on our evaluation of the data, we anticipate Cohort 3 to be the final cohort in the Phase 1b trial, with preliminary data expected in the second quarter of 2021.

The two completed cohorts consisted of 16 volunteers, randomized 3:1 to receive KarXT or placebo. As part of the flexible dosing protocol, a volunteer's dose was increased if they were tolerating KarXT well at the time of the potential dose increase, as determined by the clinician. In both cohorts, healthy elderly volunteers achieved mean xanomeline blood levels comparable to, or slightly higher than, the mean xanomeline blood levels reported in our EMERGENT-1 trial, which had demonstrated a statistically significant reduction in total PANSS score in adults with schizophrenia. The majority of healthy elderly volunteers in both cohorts were titrated to xanomeline doses of 150 to 200 mg when dosed with KarXT three times per day. Data from the two completed cohorts suggest that a lower dose ratio of trospium to xanomeline, compared to the ratios used in the previous trials in healthy adult volunteers and in adults with schizophrenia, was better tolerated by healthy elderly volunteers. We believe factors including lower body weight, metabolism rate, and drug excretion rates of the healthy elderly volunteers in these cohorts may allow lower oral doses to achieve target drug exposure levels compared to other populations.

Cholinergic and anticholinergic AEs seen in Cohorts 1 and 2 were similar to those observed in prior trials of KarXT. The vast majority of AEs (>80%) were rated as mild and no syncopal events were observed. In Cohort 1, one serious adverse event, or SAE, of urinary retention was reported related to the higher dose of trospium used in Cohort 1. In Cohort 2, which utilized a lower trospium dose, all AEs were rated mild or moderate in severity and there were no SAEs. Cohort 3 will serve to further refine the dose range of xanomeline and trospium and titration protocol.

The design of the trial is similar to our previously completed Phase 1 dose-ranging trial in healthy adult volunteers that was used to select doses for EMERGENT-1, our completed Phase 2 trial in adults with schizophrenia. In our previously completed Phase 1 trial of healthy adults, we enrolled four cohorts of volunteers and evaluated a range of xanomeline and trospium doses, including xanomeline doses that exceeded the doses selected for the subsequently completed the Phase 2 EMERGENT-1 trial. Further, our proprietary formulation of KarXT led to an approximate 10% increase in blood levels of xanomeline compared to prior xanomeline only formulations that were evaluated by Eli Lilly and Company.

Based on data from Cohorts 1 and 2 from the on-going trial, we believe that potentially therapeutic doses of KarXT can be administered to elderly adults using titration and flexible dosing while maintaining a favorable tolerability profile to provide a path to a Phase 2 trial evaluating KarXT in DRP. We have commenced planning for this Phase 2 DRP trial, and we expect to provide further guidance following the completion of Cohort 3 later this year.

Planned Additional Formulations of KarXT

We believe that additional formulations of KarXT have the potential to further improve the therapeutic window of KarXT and offer patient compliance advantages through decreased dosing frequency. Our ongoing research efforts include the development of advanced oral, long-acting injectable, transdermal and buccal formulations. We plan to have an additional oral formulation of KarXT in Phase 1 clinical trials in 2021.

Other Research Programs

We continue to build our early stage pipeline. We currently have a novel series of compounds focused on muscarinic receptor targets. In particular, we have synthesized lead compounds for further development as potential therapeutic agents in several CNS disorders, including schizophrenia and DRP. We have completed in vitro screening for several compounds and advanced these lead compounds for further preclinical development. In vivo evaluation of these compounds in rodents is ongoing for these indications, and we expect to initiate IND-enabling studies in 2021. We believe we can optimize these compounds and advance their development through preclinical studies and into clinical development, given our expertise in this space. In February 2020 we announced a drug discovery partnership with Charles River Laboratories to accommodate continued growth in our muscarinic receptor drug discovery efforts. In July 2020 we announced a drug discovery collaboration with Psychogenics, Inc. to discover novel drug candidates for the treatment of neuropsychiatric disorders. We continue to evaluate other opportunities focused on muscarinic and non-muscarinic targets for CNS disorders.

Manufacturing and Supply

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently source all of our nonclinical and clinical compound supply through third-party contract manufacturing/ organizations, or CMOs. We have established a robust supply chain to enable sufficient supply of the raw materials needed to conduct our EMERGENT program, as well as support NDA application. We continue to expand our manufacturing network to ensure redundant supply of critical input materials.

For clinical supply, we use CMOs who act in accordance with the FDA's good laboratory practices, or GLP, and current good manufacturing practices, cGMP, for the manufacture of drug substance and product. Currently, we contract with Neuland Laboratories Limited and Regis Technologies, Inc., for the manufacture of xanomeline and source trospium from Procos, S.p.A. We expect to rely on third parties for our manufacturing processes and the production of all clinical supply drug substance and drug product. We use additional contract manufacturers to fill, label, package, store and distribute investigational drug products. It is our intent to identify and qualify additional manufacturers to provide active pharmaceutical ingredient and fill-and-finish services prior to submission of a new drug application to the FDA for any product candidates that complete clinical development.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions and governmental agencies as well as public and private research institutions. Any product candidates that we successfully develop and commercialize, including KarXT, may compete with existing therapies and new therapies that may become available in the future.

Our competitors may have significantly greater financial resources, established presence in the market, expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific, sales, marketing and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of KarXT, and any other product candidates that we develop to address CNS disorders, if approved, are likely to be efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Psychosis in patients with schizophrenia

There are currently no FDA-approved drugs for the negative or cognitive symptoms of schizophrenia. The current standards of care for the psychotic symptoms of patients with schizophrenia are antipsychotic treatments that work primarily by inhibiting D2 dopamine and 5HT2-A serotonin receptors as their primary mechanism of action. These drugs include: Abilify, marketed by Bristol-Myers Squibb Company, Zyprexa, marketed by Eli Lilly, Vraylar, marketed by Allergan, Clozaril, marketed by Mylan Products Ltd., Latuda, marketed by Sumitomo Dainippon Pharma Co., Ltd., and Caplyta, marketed by Intra-Cellular Therapies, Inc. Many of these drugs are prescribed for a variety of neuropsychiatric conditions, including bipolar disorder, depression and Tourette syndrome. Additionally, we are aware of several product candidates in clinical development that are designed to modulate dopamine and/or serotonin receptors including product candidates being developed by Alkermes plc, ACADIA Pharmaceuticals Inc., Sunovion Pharmaceuticals, Inc. and Cerevel Therapeutics, LLC.

Dementia-Related Psychosis

There are currently no approved treatments for DRP, including psychosis related to AD. Patients with DRP are commonly treated with antipsychotic medications that are indicated and approved for schizophrenia. Currently, there is one drug, marketed and developed by Acadia Pharmaceuticals, for which the FDA is evaluating an sNDA application for marketing authorization for the treatment of DRP. Available treatments for AD patients are only indicated for enhancing cognition in AD patients, and include acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine and memantine. These medications are available generically although specific dosage forms and combinations are proprietary and marketed by large pharmaceutical companies such as, Allergan, Janssen Pharmaceuticals NV, Novartis International AG and Pfizer Inc.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including pursuing and maintaining patent protection intended to cover our product candidate and their methods of use, as well as other inventions that are important to our business. In addition to patent protection, we also rely on trade secrets to protect aspects of our business that we do not consider appropriate for patent protection.

Our commercial success depends in part upon our ability to obtain and maintain patent and other proprietary protection for commercially important technologies, inventions and know-how related to our business, defend and enforce our intellectual property rights, particularly our patent rights, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable intellectual property rights of others.

The patent positions for biotechnology companies like us are generally uncertain and can involve complex legal, scientific and factual issues. In addition, the coverage claimed in a patent application can be significantly reduced before a patent is issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our platform technologies and product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Product Candidates

With regard to our KarXT product candidate, we exclusively license from PureTech Health LLC, or PureTech Health, a patent family comprising two issued U.S. patents with claims directed to an oral medicament comprising certain doses of xanomeline and/or the salt thereof and certain doses of trospium chloride, three issued U.S. patents with claims directed to methods for treating central nervous system disorders using an oral medicament comprising certain doses of xanomeline and/or salts thereof and certain doses of trospium chloride, issued patents in Canada, Europe, and Hong Kong, and a total of four patent applications pending, one in each of the U.S., Europe, Japan, and Hong Kong. The patents and the pending

patent applications, if issued, are expected to expire in 2030 without taking into account a possible Patent Term Extension, or PTE, or any possible patent term adjustments. We also own one issued U.S. patent and three pending U.S. patent applications, one of which is allowed, and a pending PCT application with claims directed towards an oral pharmaceutical composition, comprising a plurality of xanomeline beads having a core comprising xanomeline or a salt thereof, and a plurality of trospium beads having a core comprising a salt of trospium. The patent and the pending patent applications, if issued, are expected to expire in 2039 without taking into account a possible PTE or any possible patent term adjustments. We also own one pending U.S. non-provisional patent application and one pending PCT application with claims directed to the use of KarXT for treating schizophrenia or a disease related to schizophrenia in a patient in need thereof. The patent applications, if issued, are expected to expire in 2040 without taking into account a possible PTE or any possible patent term adjustments. We also own two pending U.S. provisional patent applications, one pending U.S. patent application, and two PCT applications with claims directed to compounds targeting muscarinic receptors and methods of treatment using such compounds. The patent applications claiming priority to and the benefit of these provisional applications, if issued, are expected to expire in 2040 or 2041 without taking into account a possible PTE or any possible patent term adjustments. Our U.S. and foreign patent applications also disclose other muscarinic activators in combination with other muscarinic inhibitors to treat CNS disorders.

License Agreements

License Agreement with Eli Lilly and Company

In May 2012, we entered into an exclusive license agreement, or the Lilly License Agreement, with Eli Lilly, pursuant to which Eli Lilly assigned to us all of its rights to certain patents (now expired), regulatory documentation, data records and materials related to xanomeline. We are also entitled to sublicense or otherwise transfer the rights granted in connection with the Lilly License Agreement.

Under the Lilly License Agreement, we are obligated to use commercially reasonable efforts to develop, manufacture, commercialize and seek and maintain regulatory approval for xanomeline, in any formulation, for use in humans.

We paid Eli Lilly an upfront payment of $100,000 and have agreed to make milestone payments to Eli Lilly of up to an aggregate of $16 million upon the achievement of specified regulatory milestones and up to an aggregate of $54 million in commercial milestones. In addition, we are obligated to pay Eli Lilly tiered royalties, at rates in the low to mid single-digit percentages, on the worldwide net sales of any commercialized product on a country-by-country basis until the expiration of the applicable royalty term, which is the longer of six years from the date of first commercial sale of each licensed product within a country or data exclusivity in such country. During the royalty term, Eli Lilly is prohibited from granting any third-party rights to the patents, regulatory documentation, data records and materials that have been licensed to us under the Lilly License Agreement.

The Lilly License Agreement will expire on the later of (i) the expiration of the last-to-expire royalty term on a licensed product-by-licensed product basis or (ii) the date on which we have made all milestone payments pursuant to the terms of the Lilly License Agreement, unless terminated earlier by the parties. In no event will the term of the Lilly License Agreement exceed 15 years past the anniversary of the first commercial sale of a xanomeline product. We may terminate the Lilly License Agreement for any reason with proper prior notice to Eli Lilly. Either party may terminate the Lilly License Agreement upon an uncured material breach by the other party.

Patent License Agreement with PureTech Health LLC

In March 2011, we entered into an exclusive license agreement, or the Patent License Agreement, with PureTech Health, pursuant to which PureTech Health granted us an exclusive license to patent rights relating to combinations of a muscarinic activator with a muscarinic inhibitor for the treatment of central nervous system disorders.

In connection with the Patent License Agreement, we have agreed to make milestone payments to PureTech Health of up to an aggregate of $10 million upon the achievement of specified development and regulatory milestones, of which we paid PureTech Health a milestone payment of $2 million in 2020. No other milestone payments have been made under this agreement. In addition, we are obligated to pay PureTech Health low single-digit royalties on the worldwide net sales of any commercialized product covered by the licenses granted under the Patent License Agreement. In the event that we sublicense any of the patent rights granted under the Patent License Agreement, we will be obligated to pay PureTech Health royalties within the range of 15% to 25% on any income we receive from the sublicensee, excluding royalties.

We may terminate the Patent License Agreement for any reason with proper prior notice to PureTech Health. Either party may terminate the Patent License Agreement upon an uncured material breach by the other party.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The failure to comply with applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities. In addition, an applicant may need to recall a product.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of nonclinical, or preclinical, laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an investigational new drug application, or IND, which must take effect before human clinical trials may begin;
- approval by an independent Institutional Review Board, or IRB, representing each clinical site before each clinical trial may be initiated at that site;

- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of a new drug application, or NDA, and payment of user fees;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practice, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- FDA review and approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a compound in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of the investigational drug. In an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments. In addition, the results of the preclinical tests, manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study is conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. FDA must also be able to validate the data from the study through an on-site inspection if necessary.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review of the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the subjects or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects, or their legal representative, provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- *Phase 1*. The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
- *Phase 2*. The drug is administered to 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 optimal dosage.
- *Phase 3*. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.
- *Phase 4*. Post-approval studies may be conducted after initial regulatory approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA. In addition, within 15 calendar days after the sponsor determines that the information qualifies for reporting, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, 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. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as 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 drug candidate and, among other things, the applicant must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Combination Rule

The FDA's Combination Rule governing fixed combination drug products provides that two or more drugs may be combined in a single dosage form when each component contributes to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. This rule is meant to ensure that any fixed-dose combination drug provides an advantage to the patient over and above that obtained when one of the individual ingredients is used in the usual safe and effective dose.

Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to a significant application user fee as well as annual prescription drug product program fees. These fees are typically increased annually. Certain exceptions and waivers are available for some of these fees.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt, before accepting the NDA for filing, to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Applications for drugs containing new molecular entities are meant to be reviewed within ten months from the date of filing, and applications for "priority review" products containing new molecular entities are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

During its review of an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an NDA 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.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, 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.

Fast Track, Breakthrough Therapy, and Priority Review

The FDA has a number of programs intended to facilitate and expedite development and review of new drugs if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. Three of these programs are referred to as fast track designation, breakthrough therapy designation, and priority review designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either 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 FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious or life-threatening disease or condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, could result in the FDA's withdrawal of the approval and require the withdrawal of the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities and select clinical trial sites, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If a complete response letter is issued, the applicant may resubmit the NDA to address all of the deficiencies identified in the letter, withdraw the application, or request a hearing. If the applicant resubmits the NDA, only when the deficiencies have been addressed to the FDA's satisfaction will the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on

the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety or effectiveness after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, many changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are annual prescription drug product program fee requirements for certain marketed products.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the NDA holder and any third-party manufacturers that the NDA holder may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or voluntary product recalls;
- fines, warning or untitled letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. 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 liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Hatch-Waxman Amendments

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A 505(b)(2) NDA is an application that contains full reports of investigations of safety and efficacy but where at least some of the information required for approval comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This regulatory pathway enables the applicant to rely, in part, on the FDA's prior findings of safety and efficacy for an existing product, or published literature, in support of its application. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, to a previously approved product, known as a reference listed drug, or RLD. ANDAs are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through *in vitro*, *in vivo*, or other testing. The generic version must deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug.

Non-Patent Exclusivity

Under the Hatch-Waxman Amendments, the FDA may not approve (or in some cases accept) an ANDA or 505(b)(2) application until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity, or NCE. For the purposes of this provision, an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, which states the proposed generic drug will not infringe one or more of the already approved product's listed patents or that such patents are invalid or unenforceable, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity for non-NCE drugs if the NDA or a supplement to the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application or supplement. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication, but it generally would not protect the original, unmodified product from generic competition. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product; it only prevents FDA from approving such ANDAs.

Hatch-Waxman Patent Certification and the 30-Month Stay

In seeking approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Upon approval, each of the patents listed by the NDA sponsor is published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Upon submission of an ANDA or 505(b)(2) NDA, an applicant is required to certify to the FDA concerning any patents listed for the RLD in the Orange Book that:

- no patent information on the drug product that is the subject of the application has been submitted to the FDA;
- such patent has expired;
- the date on which such patent expires; or
- such patent is invalid, unenforceable or will not be infringed upon by the manufacture, use, or sale of the drug product for which the application is submitted.

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through the last type of certification, also known as a paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all of the listed patents claiming the referenced product have expired. If the ANDA or 505(b)(2) NDA applicant has provided a paragraph IV certification the applicant must send notice of the paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. If the paragraph IV certification is challenged by an NDA holder or the patent owner(s) asserts a patent challenge to the paragraph IV certification, the FDA may not approve that application until the earlier of 30 months from the receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent was favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. In instances where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owner(s) regularly take action to trigger the 30-month stay, recognizing that the related patent litigation may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation. If the drug has NCE exclusivity and the ANDA is submitted four years after approval, the 30-month stay is extended so that it expires seven and a half years after approval of the innovator drug, unless the patent expires or there is a decision in the infringement case that is favorable to the ANDA applicant before then.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent term restoration of up to seven and a half years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date, provided the sponsor acted with diligence. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question and within 60 days of drug approval. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU Member States govern the system for the approval of clinical trials in the European Union. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation) was adopted. The Clinical Trials Regulation will be directly applicable in all the EU Member States (without national implementation) following confirmation of the full functionality of the Clinical Trials Information System, the centralized EU portal and database for clinical trials foreseen by the new Regulation, through an independent audit. This is currently expected to occur in December 2021. Conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the “EU portal”; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The United Kingdom has implemented Directive 2001/20/EC into national law through the Medicines for Human Use (Clinical Trials) Regulations, so the United Kingdom’s regulation of clinical trials is currently aligned with EU regulations. Whether the United Kingdom will amend its legislation to align more closely with the new EU Regulation once that comes into effect is as yet unknown.

Marketing Authorization

To obtain a marketing authorization for a product under European Union regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the European Medicines Agency, or EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU Member States and Iceland, Liechtenstein and Norway. Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of HIV or AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases. For products with a new active substance indicated for the treatment of other diseases and products that are a significant therapeutic, scientific or technical innovation and whose authorization would be in the interest of public health at EU level, the centralized procedure is optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 67 days from the date of the CHMP Opinion, the European Commission will adopt its final decision on the marketing authorization application.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Under the above described procedures, before granting the marketing authorizations, the EMA or the competent authorities of the Member States of the European Economic Area (EEA) make an assessment of the risk-benefit balance of the drug on the basis of scientific criteria concerning its quality, safety, and efficacy.

Now that the United Kingdom has left the EU, Great Britain will no longer be covered by centralized marketing authorizations (under the Northern Irish Protocol, centralized EU authorizations will continue to be recognized in Northern Ireland). All medicinal products with a current centralized authorization were automatically converted to Great Britain's marketing authorizations on January 1, 2021. For a period of two years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required. The MHRA also has the power to have regard to marketing authorizations approved in EEA Member States through Decentralized or Mutual Recognition Procedures with a view to more quickly granting a marketing authorization in the United Kingdom or Great Britain.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the European Union market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the European Union market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the European Union is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the European Union's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable European Union laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with European Union cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union notably under Directive 2001/83/EC, as amended, and EU Member State laws.

European Data Collection Regulation

In the event we decide to conduct clinical trials in the European Union, we may be subject to additional privacy restrictions. The collection and use of personal health information in the European Union is governed by the provisions of the Data Protection Directive, and as of May 25, 2018, the General Data Protection Regulation, or GDPR. This directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the United States. Failure to comply with the requirements of the Data Protection Directive (which governs the collection and use of personal health data in the European Union), the GDPR, and the related national data protection laws of the EU Member States may result in fines and other administrative penalties. The GDPR introduced new data protection requirements in the EU and substantial fines for breaches of the data protection rules. The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

In addition, further to the United Kingdom's (UK) exit from the EU on January 31, 2020, the GDPR ceased to apply in the UK at the end of the transition period on December 31, 2020. However, as of January 1, 2021, the UK's European Union (Withdrawal) Act 2018 incorporated the GDPR (as it existed on December 31, 2020 but subject to certain UK specific amendments) into UK law (referred to as the 'UK GDPR'). The UK GDPR and the UK Data Protection Act 2018 set out the UK's data protection regime, which is independent from but aligned to the EU's data protection regime. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher. The UK, however, is now regarded as a third country under the EU's GDPR which means that transfers of personal data from the EEA to the UK will be restricted unless an appropriate safeguard, as recognised by the EU's GDPR, has been put in place. Although, under the EU-UK Trade Cooperation Agreement it is lawful to transfer personal data between the UK and the EEA for a 6 month period following the end of the transition period, with a view to achieving an adequacy decision from the European Commission during that period. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection (this means that personal data transfers from the UK to the EEA remain free flowing).

Healthcare and Privacy Laws and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching hospitals and patient privacy laws and regulations and other

healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare and privacy laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid; a person or entity need not have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim that includes 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. On November 20, 2020, OIG finalized further modifications to the federal Anti-Kickback Statute. Under the final rules, OIG added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others. These rule (with exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business;
- the federal civil and criminal false claims laws, including the civil False Claims Act, or FCA, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent; knowingly making a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The FCA also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal civil and criminal laws that prohibit, 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 by any trick or device 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;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, 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 attorneys' fees and costs associated with pursuing federal civil actions;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, or HHS, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers;
- many state laws govern the privacy of personal information in specified circumstances, for example, in California the California Consumer Privacy Act (CCPA), which will go into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. While clinical trial data and information governed by HIPAA are currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope; and
- some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers, marketing expenditures, and drug pricing information. Certain state and local laws require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the European Union General Data Protection Regulation, also govern 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.

Pharmaceutical Insurance Coverage and Healthcare Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, the product. In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. The process for determining whether a third-party payor will provide coverage for a product may be separate from

the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Additionally, companies may also need to provide discounts to purchasers, private health plans or government healthcare programs. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a third-party payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party payor reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical products, limiting coverage and the amount of reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States. For example, in March 2010, the United States Congress enacted the Affordable Care Act, which, among other things, includes contains to the coverage and payment for products under government health care programs. The Affordable Care Act includes provisions of importance to our potential product candidates, including among other things, that:

- created an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs;
- expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount, which was increased to 70% by the Bipartisan Budget Act of 2018 (as of January 1, 2019), off the negotiated price of applicable brand drugs to eligible

beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and

- 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.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been judicial and Congressional challenges to certain provisions of the Affordable Care Act, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the Affordable Care Act such as removing penalties, starting January 1, 2019, for not complying with the Affordable Care Act's individual mandate to carry health insurance, delaying the implementation of certain Affordable Care Act-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

In addition, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their commercial products, which has resulted in several Congressional inquiries and proposed and enacted state and federal 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 pharmaceutical products. For example, at the federal level, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. While some proposed measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing Reduction Action of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. An even more restrictive bill, the Lower Drug Costs Now Act of 2019, was introduced in the House of Representatives on September 19, 2019, and would require the Department of Health and Human Services (HHS) to directly negotiate drug prices with manufacturers. It is unclear whether either of these bills will make it through both chambers and be signed into law, and if either is enacted, what effect it would have on our business. Individual states in the United States have also

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.

Outside the United States, ensuring coverage and adequate payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to government control in many countries. Pricing negotiations with government authorities can extend well beyond the receipt of regulatory approval for a product and may require a clinical trial that compares the cost-effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on healthcare costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Legal Proceedings

We are not currently subject to any material legal proceedings.

Facilities

Our headquarters are located at 33 Arch Street, Suite 3110, Boston, Massachusetts, where we occupied approximately 11,225 square feet of leased office space as of December 31, 2020. This lease expires in December 2023.

Additionally, we maintain offices located at 11711 N. Meridian Street, Suite 430, Carmel, Indiana, consisting of 5,050 square feet of leased office space. This lease expires in July 2023.

Employees

As of February 15, 2021, we had 63 full-time employees, including a total of 23 employees with M.D. and/or Ph.D. degrees. Of our workforce, 44 employees are directly engaged in research and development with the rest providing administrative, business and operations support. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider the relationship with our employees to be good.

Human Capital

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees, advisors and consultants. The principal purposes of our equity incentive plans are to attract, retain and reward personnel through the granting of equity-based compensation awards in order to increase shareholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

Corporate Information

We were incorporated under the laws of the State of Delaware in July 2009 as Karuna Pharmaceuticals, Inc. In March 2019, the Company changed its name to Karuna Therapeutics, Inc. Our principal corporate office is located at 33 Arch Street, Suite 3110, Boston, Massachusetts. Our website address is www.karunatx.com. The information on our website is not incorporated by reference in this Annual Report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended, or the Exchange Act. These include our Annual Reports on Form 10-K, our Quarterly Reports on Form 10-Q, and our Current Reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding us and other issuers that file electronically with the SEC. The SEC's Internet website address is http://www.sec.gov.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," in evaluating our company and our business. If any of the following risks actually occur, our business, financial condition, results of operations and growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to Our Financial Position and Need for Capital

We are a clinical-stage biopharmaceutical company and we have incurred significant losses since our inception. We anticipate that we will continue to incur significant losses for the foreseeable future.

Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate effect or an acceptable safety profile, gain regulatory approval and become commercially viable. We have no products approved for commercial sale and have not generated any revenue from product sales to date, and we will continue to incur significant research and development and other expenses related to our clinical development and ongoing operations. As a result, we are not profitable and have incurred losses in each period since our inception. Since our inception, we have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical trials. Our financial condition and operating results, including net losses, may fluctuate significantly from quarter to quarter and year to year. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance. Additionally, net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. Our net losses were $68.6 million, $44.0 million and $17.5 million for the years ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $144.1 million. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for, KarXT in our initial and potential additional indications as well as for other product candidates.

We anticipate that our expenses will increase substantially if and as we:

- continue to develop and conduct clinical trials for KarXT for our initial and potential additional indications;
- initiate and continue research and development, including preclinical, clinical, and discovery efforts for any future product candidates;
- seek to identify additional product candidates;
- seek regulatory approvals for KarXT, or any other product candidates that successfully complete clinical development;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development and our ongoing operations as a public company;
- hire and retain additional personnel, such as clinical, quality control, scientific, commercial and administrative personnel;
- maintain, expand and protect our intellectual property portfolio;
- establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval;

- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other product candidates and technologies.

Our expenses could increase beyond our expectations if we are required by the U.S. Food and Drug Administration, or FDA, or other regulatory authorities to perform clinical trials in addition to those that we currently expect, or if there are any delays in establishing appropriate manufacturing arrangements for or in completing our clinical trials or the development of any of our product candidates.

We have never generated revenue from product sales and may never be profitable.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue, if any, unless and until we, either alone or with a collaborator, are able to obtain regulatory approval for, and successfully commercialize, KarXT for our initial and potential additional indications, or any other product candidates we may develop, license or acquire. Successful commercialization will require achievement of many key milestones, including demonstrating safety and efficacy in clinical trials, obtaining regulatory, including marketing, approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our future collaborators, may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately and precisely predict the timing and amount of revenues, the extent of any further losses or if or when we might achieve profitability. We and any future collaborators may never succeed in these activities and, even if we do, or any future collaborators do, we may never generate revenues that are large enough for us 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. Additionally, our expenses could increase if we are required by the FDA or any comparable foreign regulatory authority to perform clinical trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates.

Our failure to become and remain profitable may depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If we continue to suffer losses as we have in the past, investors may not receive any return on their investment and may lose their entire investment.

We have a limited operating history, which may make it difficult to evaluate the prospects for our future viability.

Our operations to date have been limited to organizing, staffing and financing our company, raising capital, in-licensing our technology and conducting research and development activities, including preclinical studies and clinical trials, for our product candidates. We have not yet demonstrated an ability to generate revenues, 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. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in clinical development, especially clinical-stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will eventually need to transition from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the preclinical and clinical development of our current and future programs. If we are able to gain marketing approval for product candidates that we develop, including any indication for which we are developing or may develop KarXT, we will require significant additional amounts of cash in order to launch and commercialize such product candidates to the extent that such launch and commercialization are not the responsibility of a future collaborator that we may contract with in the future. In addition, other unanticipated costs may arise in the course of our development efforts. Because the design and outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of any product candidate we develop.

Our future capital requirements depend on many factors, including:

- the scope, progress, results and costs of researching and developing KarXT for our initial and potential additional indications, as well as other product candidates we may develop;
- the timing of, and the costs involved in, obtaining marketing approvals for KarXT for our initial and potential additional indications, and other product candidates we may develop and pursue;
- the number of future product candidates that we may pursue and their development requirements;
- if approved, the costs of commercialization activities for KarXT for any approved indications, or any other product candidate that receives regulatory approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of regulatory approval, revenue, if any, received from commercial sales of KarXT for any approved indications or any other product candidates;
- the extent to which we in-license or acquire rights to other products, product candidates or technologies;
- our headcount growth and associated costs as we expand our research and development, increase our office space, and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights, including enforcing and defending intellectual property related claims; and
- the ongoing costs of operating as a public company.

We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. Any of our current or future license agreements may also be terminated if we are unable to meet the payment or other obligations under the agreements.

We believe that our existing cash, cash equivalents and available-for-sale investments as of December 31, 2020, will enable us to fund our operating expenses and capital expenditure requirements into 2023. Our estimate may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned.

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

We expect our expenses to increase in connection with our planned operations. Unless and until we can generate a substantial amount of revenue from our product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings, collaborations, licensing arrangements or other sources, or any combination of the foregoing. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, your ownership interest may be diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect your rights as a common stockholder. In addition, debt financing, if available, may result in fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

If we raise additional funds through collaborations or marketing, distribution, licensing and royalty arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds 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 product candidates that we would otherwise prefer to develop and market ourselves.

Our ability to use net operating losses and research and development credits to offset future taxable income may be subject to certain limitations.

As of August 1, 2018, PureTech no longer held 80% of the outstanding shares of the Company. Therefore, from that date onward, the Company was required to file a separate U.S. federal income tax return. On July 2, 2019, PureTech no longer held 50% of the outstanding shares of the Company. As such, we have filed separate state income tax returns subsequent to this date. At December 31, 2020, on a separate return method, we had federal net operating loss carryforwards totaling $179.8 million of which $9.7 million begin to expire in 2029 and $170.1 million can be carried forward indefinitely. In addition, we had state net operating loss carryforwards totaling $151.7 million which begin to expire in 2030. Lastly, we also had federal and state research and development tax credit carryforwards of $5.0 million and $0.8 million which begin to expire in 2031. Because the Company had historically been a subsidiary of PureTech, $179.4 million and $131.7 million of the federal and state net operating loss carryforwards, respectively, can be used to offset income on our future tax returns. In addition, $4.9 million and $0.8 million of the federal and state tax credit carryforwards, respectively, can be used to offset tax due on our future tax returns. Our net operating loss and tax credit carryforwards could, in whole or in part, expire unused and be unavailable to offset future income tax liabilities.

In addition, in general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses or tax credits, or NOLs or credits, to offset future taxable income or taxes. For these purposes, an ownership change generally occurs where the aggregate stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation's stock increases its ownership by more than 50 percentage points over its lowest ownership percentage within a specified testing period. We have completed a Section 382 study during the year ended December 31, 2020, and while certain tax attributes are subject to annual limitations, none are expected to be restricted in their future utilization if the Company earns sufficient future profits to utilize the tax attributes. If an ownership change does occur in the future, existing NOLs or credits may be subject to such limitations. Our NOLs or credits may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs or credits and as a result it is possible that a limitation on our ability to use our historical NOLs or credits could harm our future operating results by effectively increasing our future tax obligations.

Furthermore, our ability to utilize our NOLs or credits is conditioned upon our attaining profitability and generating U.S. federal and state taxable income. As described above under "—Risks Related to Our Financial Position and Need for Additional Capital," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; and therefore, we do not know whether or when we will generate the U.S. federal or state taxable income necessary to utilize our NOL or credit carryforwards that are subject to limitation by Sections 382 and 383 of the Code.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

Our business substantially depends upon the successful development of KarXT. If we are unable to obtain regulatory approval for, and successfully commercialize, KarXT, our business may be materially harmed.

We currently have no products approved for sale and are investing the majority of our efforts and financial resources in the development of our lead product candidate, KarXT for psychosis in patients with schizophrenia and dementia-related psychosis, or DRP. Successful continued development and ultimate regulatory approval of KarXT for our initial and potential additional indications is critical to the future success of our business. We will need to raise sufficient funds for, and successfully enroll and complete, our clinical development programs of KarXT for psychosis in patients with schizophrenia and DRP, and possibly other diseases. The future regulatory and commercial success of KarXT is subject to a number of risks, including the following:

- successful completion of preclinical studies and clinical trials;
- successful patient enrollment in clinical trials;
- successful efficacy data from our clinical programs that support acceptable risk-benefit profiles of our product candidates in the intended populations;
- receipt and maintenance of marketing approvals from applicable regulatory authorities;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our product candidates;
- entry into collaborations to further the development of our product candidates;
- establishing sales, marketing and distribution capabilities and commercial launch of our products, if and when approved, whether alone or in collaboration with others;
- successful commercial launch of our product candidates, if and when approved;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors;
- obtaining and maintaining third-party insurance coverage and adequate reimbursement;
- maintaining a continued acceptable safety profile of the products following approval;

- effectively competing with other therapies; and
- enforcing and defending intellectual property rights and claims.

Many of these risks are beyond our control, including the risks related to clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any future collaborator. If we are unable to develop, receive regulatory approval for, or successfully commercialize KarXT for the indications we are developing it for, or if we experience delays as a result of any of these risks or otherwise, our business could be materially harmed.

In addition, of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a new drug application, or NDA, to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval for KarXT for any indication, any such approval may be subject to limitations on the indications or uses or patient populations for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure you that we will successfully develop or commercialize KarXT for any indication. If we or any of our future collaborators are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize KarXT for our initial or potential additional indications, we may not be able to generate sufficient revenue to continue our business. In addition, our failure to demonstrate positive results in our clinical trials in any indication for which we are developing KarXT could adversely affect our development efforts for KarXT in other indications.

We have never commercialized a product candidate and may experience delays or unexpected difficulties in obtaining regulatory approval for KarXT for our initial or potential additional indications.

We have never obtained regulatory approval for, or commercialized, a drug. It is possible that the FDA may refuse to accept any or all of our planned NDAs for substantive review or may conclude after review of our data that our application is insufficient to obtain regulatory approval for any product candidates. If the FDA does not approve any of our planned NDAs, it may require that we conduct additional costly clinical, nonclinical or manufacturing validation studies before it will reconsider our applications. Depending on the extent of these or any other FDA-required studies, approval of any NDA or other application that we submit may be significantly delayed, possibly for several years, or may require us to expend more resources than we have available. Any failure or delay in obtaining regulatory approvals would prevent us from commercializing KarXT for any indication or any other product candidate, generating revenues and achieving and sustaining profitability. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA to approve any NDA or other application that we submit. If any of these outcomes occur, we may be forced to abandon the development of our product candidates, which would materially adversely affect our business and could potentially cause us to cease operations. We face similar risks for our applications in foreign jurisdictions. In addition, difficulties in obtaining approval of KarXT in any of the initial indications for which we are developing it could adversely affect our efforts to seek approval from regulatory authorities for KarXT in other indications.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time-consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

We, and any future collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining regulatory approval from the FDA. Foreign regulatory authorities, such as the European Medicines Agency, or EMA, impose similar requirements. The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable, but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. To date, we have not submitted an NDA to the FDA or similar drug approval submissions to comparable foreign regulatory authorities for KarXT or any other product candidate. We, and any future collaborators, must complete additional preclinical or nonclinical studies and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of KarXT for our initial and potential additional indications or other product candidates is susceptible to the risk of failure inherent at any stage of development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements, and determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or is not approvable. It is possible that even if KarXT or any other product candidate has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of KarXT or any other product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by KarXT or any other product candidate, or mistakenly believe that our product candidates are toxic or not well-tolerated when that is not in fact the case.

Our current and future product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree as to the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate’s clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from clinical trials or preclinical studies;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA to the FDA or other submission or to obtain regulatory approval in the United States, the European Union or elsewhere;
- the FDA or comparable foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of clinical trial results may result in our failing to obtain regulatory approval to market any product candidate we develop, which would significantly harm our business, results of operations and prospects. There is no assurance that the endpoints and trial designs used for the approval of currently approved CNS drugs will be acceptable for future approvals, including for KarXT. The FDA and other comparable foreign authorities have substantial discretion in the approval process, and determining when or whether regulatory approval will be obtained for any product candidate that we develop. Even if we believe the data collected from future clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA or any other regulatory authority.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

We may incur unexpected costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

To obtain the requisite regulatory approvals to commercialize any of our product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our product candidates are safe and effective in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process and our future clinical trial results may not be successful.

We may experience delays in completing our clinical trials or preclinical studies and initiating or completing additional clinical trials. We may also experience numerous unforeseen events during our clinical trials that could delay or prevent our ability to receive marketing approval or commercialize the product candidates we develop, including:

- regulators, or institutional review boards, or IRBs, or other reviewing bodies may not authorize us or our investigators to commence a clinical trial, or to conduct or continue a clinical trial at a prospective or specific trial site;
- we may not reach agreement on acceptable terms with prospective contract research organizations, or 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;
- the number of subjects or patients required for clinical trials of KarXT in an indication or any other product candidate may be larger than we anticipate, enrollment in these clinical trials may be insufficient or slower than we anticipate, and the number of clinical trials being conducted at any given time may be high and result in fewer available patients for any given clinical trial, or patients may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including those manufacturing our product candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have to amend a clinical trial protocol submitted to regulatory authorities or conduct additional studies to reflect changes in regulatory requirements or guidance, which we may be required to resubmit to an IRB and regulatory authorities for re-examination;
- regulators, IRBs or other reviewing bodies may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreement for clinical and commercial supplies, or the supply or quality of KarXT or any other product candidate or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and
- the potential for approval policies or regulations of the FDA or the applicable foreign regulatory agencies to significantly change in a manner rendering our clinical data insufficient for approval.

Regulators, IRBs of the institutions in which clinical trials are being conducted or data monitoring committees may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. For example, a previous Phase 1 clinical trial of KarXT conducted by us was put on hold by the FDA in April 2017 after one and half days of dosing due to preliminary assessment of preclinical findings. Although this hold was lifted in August 2017 after the FDA's complete review of the preclinical data and our proposed addition of monitoring for potential decreased gastrointestinal motility to the clinical protocol, we face the risk of future clinical holds that may not be lifted in a timely manner, if at all.

Negative or inconclusive results from our planned Phase 3 EMERGENT clinical trials of KarXT for the treatment of psychosis in patients with schizophrenia, or any other clinical trial or preclinical studies in animals that we conduct, could mandate repeated or additional clinical trials and could result in changes to or delays in clinical trials KarXT in other indications. We do not know whether any clinical trials that we may conduct will demonstrate adequate efficacy and safety to result in regulatory approval to market KarXT for our initial or potential additional indications, or any other product candidate. If later stage clinical trials do not produce favorable results, our ability to obtain regulatory approval for KarXT for initial or potential additional indications, or any other product candidate, may be adversely impacted.

Our failure to successfully initiate and complete clinical trials of KarXT for our initial or potential additional indications or any other product candidate and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market KarXT or any other product candidate would significantly harm our business. Our product candidate development costs will also increase if we experience delays in testing or regulatory approvals and we may be required to obtain additional funds to complete clinical trials. We cannot assure you that our clinical trials will begin as planned or be completed on schedule, if at all, or that we will not need to restructure our trials after they have begun. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates, which may harm our business and results of operations. In addition, many of the factors that cause, or lead to, delays of clinical trials may ultimately lead to the denial of regulatory approval of KarXT or any other product candidate.

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us or any future collaboration partners from obtaining approvals for the commercialization of KarXT for our initial or potential additional indications as well as for any other product candidate we develop.

Any product candidate we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction and it is possible that none of the product candidates we may seek to develop in the future will ever obtain regulatory approval. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity, efficacy and potency. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any product candidates we develop may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity, and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any product candidates we may develop, the commercial prospects for those product candidates, including for KarXT in other indications, may be harmed, and our ability to generate revenues will be materially impaired.

Risks associated with the in-licensing or acquisition of product candidates could cause substantial delays in the preclinical and clinical development of our product candidates.

We have relied on Eli Lilly and Company, or Eli Lilly, to have conducted research and development in accordance with the applicable protocol, legal, regulatory and scientific standards, having accurately reported the results of all clinical trials conducted prior to our acquisition of the rights to xanomeline and having correctly collected and interpreted the data from these trials. If the research and development processes or the results of the development programs prior to our development of KarXT prove to be unreliable, this could result in increased costs and delays in the development of KarXT, which could adversely affect any future revenue from this product candidate.

We may also acquire or in-license additional product candidates for preclinical or clinical development or commercial sale in the future as we continue to build our pipeline. The risks associated with acquiring or in-licensing product candidates could result in delays in the commencement or completion of our preclinical studies and clinical trials, if ever, and our ability to generate revenues from our product candidates may be delayed.

The results of early-stage clinical trials and preclinical studies may not be predictive of future results. Initial data in our clinical trials may not be indicative of results obtained when these trials are completed or in later stage trials.

The results of preclinical studies may not be predictive of the results of clinical trials, and the results of any early-stage clinical trials we commence may not be predictive of the results of the later-stage clinical trials. In addition, initial data in clinical trials may not be indicative of results obtained when such trials are completed. There can be no assurance that any of our clinical trials will ultimately be successful or support further clinical development of any of our product candidates. There is a high failure rate for drugs and biologics proceeding through clinical trials. 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, and any such setbacks in our clinical development could have a material adverse effect on our business and operating results.

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 publish interim topline or preliminary data from our clinical trials. 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. Preliminary or topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could significantly harm our reputation and business prospects.

If we encounter difficulties enrolling patients in our future clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion.

Patient enrollment is affected by many factors, including:

- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the impact of the COVID-19 coronavirus pandemic;
- the design of the 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 that we are investigating;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Delays in patient enrollment may result in increased costs, affect the timing or outcome of the planned clinical trials, product candidate development and approval process and jeopardize our ability to seek and obtain the regulatory approval required to commence product sales and generate revenue, which could prevent completion of these trials, adversely affect our ability to advance the development of our product candidates, cause the value of our company to decline and limit our ability to obtain additional financing if needed. In 2019, we initiated a Phase 1b clinical trial evaluating the safety and tolerability of KarXT in healthy elderly volunteers in order to select the most appropriate dose for future KarXT trials to assess efficacy and safety in a DRP patient population. Topline results from this trial were expected by the end of 2020. However, as a result of COVID-19's impact on enrollment, we now anticipate that topline results from this trial will be announced in the second quarter of 2021. While COVID-19 has not affected the anticipated timing of our other planned clinical trials, including the initiation of the Phase 3 EMERGENT program in 2020, we continue to monitor the impact of COVID-19 across all clinical trials, particularly in the elderly population.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates proceed through preclinical studies to late-stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. For example, we are exploring other formulations and modes of administration for KarXT. Similarly, in our EMERGENT-1 trial, we used a co-formulation of KarXT, whereas previous clinical data were based on either xanomeline alone or xanomeline co-administered with trospium. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging

clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if obtained.

Undesirable side effects caused by KarXT, or any future product candidate, 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. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. In clinical trials of KarXT to date, cholinergic adverse events were generally mild or moderate in severity. However, there can be no guarantee that we would observe a similar tolerability profile of KarXT in our planned Phase 3 clinical trials or in other future clinical trials. Many compounds that initially showed promise in clinical or earlier stage testing are later found to cause undesirable or unexpected side effects that prevented further development of the compound.

If unacceptable side effects arise in the development of our product candidates, we, the FDA or comparable foreign regulatory authorities, the IRBs, or independent ethics committees at the institutions in which our trials are conducted, or the independent safety monitoring committee could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-emergent side effects that are deemed to be drug-related could also affect subject recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. Undesirable side effects in one of our clinical trials for KarXT in one indication could adversely affect enrollment in clinical trials, regulatory approval and commercialization of KarXT in other indications. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects.

Even if KarXT or any future product candidate of ours receives regulatory approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if KarXT for the treatment of any indication, or any future product candidate of ours, is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Physicians may be reluctant to take their patients off their current medications and switch their treatment regimen to KarXT. Further, patients often acclimate to the treatment regimen that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch due to lack of coverage and adequate reimbursement. In addition, even if we are able to demonstrate our product candidates' safety and efficacy to the FDA and other regulators, safety or efficacy concerns in the medical community may hinder market acceptance.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources, including management time and financial resources, and may not be successful. In particular, we may have difficulty in convincing the medical community that KarXT's preferential targeting and stimulation of certain muscarinic receptors has the potential to avoid the undesirable side effects

associated with stimulation of muscarinic receptors in the peripheral tissues. If KarXT or any other product candidate is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential advantages of the product compared to competitive therapies;
- the prevalence and severity of any side effects;
- whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy;
- our ability, or the ability of any future collaborators, to offer the product for sale at competitive prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- limitations or warnings, including distribution or use restrictions contained in the product's approved labeling;
- the strength of sales, marketing and distribution support;
- changes in the standard of care for the targeted indications for the product; and
- availability and adequacy of coverage and reimbursement from government payors, managed care plans and other third-party payors.

Any failure by KarXT or any other potential product candidate of ours that obtains regulatory approval to achieve market acceptance or commercial success would adversely affect our business prospects.

If we fail to develop and commercialize KarXT for additional indications or fail to discover, develop and commercialize other product candidates, we may be unable to grow our business and our ability to achieve our strategic objectives would be impaired.

Although the development and commercialization of KarXT for the treatment of psychosis in patients with schizophrenia and DRP is our primary focus, as part of our longer-term growth strategy, we plan to evaluate KarXT in other indications and develop other product candidates. We intend to evaluate internal opportunities from KarXT or other potential product candidates, and also may choose to in-license or acquire other product candidates as well as commercial products to treat patients suffering from other disorders with significant unmet medical needs and limited treatment options. These other potential product candidates will require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective than other commercially available alternatives.

Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including the following:

- the research methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete;
- product candidates that we develop may nevertheless be covered by third parties' patents or other exclusive rights;

- a product candidate may, on further study, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors.

If we are unsuccessful in identifying and developing additional product candidates, our potential for growth and achieving our strategic objectives may be impaired.

We may expend our resources to pursue a particular product candidate or indication and forgo the opportunity to capitalize on product candidates or indications that may ultimately be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for regulatory approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have 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 research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. 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 collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

The market for KarXT for schizophrenia and DRP and any other product candidates we may develop may be smaller than we expect.

Our estimates of the potential market opportunity for KarXT for the treatment of psychosis in patients with schizophrenia and DRP as well as any other product candidates include several key assumptions based on our industry knowledge, industry publications and third-party research reports. There can be no assurance that any of these assumptions are, or will remain, accurate. If the actual market for KarXT for these or other indications, or for any other product candidate we may develop, is smaller than we expect, our revenues, if any, may be limited and it may be more difficult for us to achieve or maintain profitability.

Competitive products may reduce or eliminate the commercial opportunity for KarXT for our current or future indications. If our competitors develop technologies or product candidates more rapidly than we do, or their technologies are more effective or safer than ours, our ability to develop and successfully commercialize KarXT may be adversely affected.

The clinical and commercial landscape for the treatment of psychosis in patients with schizophrenia and DRP is highly competitive and subject to rapid and significant technological change. We face competition with respect to our indications for KarXT and will face competition with respect to any other drug candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of drug candidates for the treatment of the indications that we are pursuing. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Although there are no FDA-approved drugs for the negative and cognitive symptoms of schizophrenia, many large pharmaceutical companies market FDA-approved drugs for the treatment of the psychotic symptoms of schizophrenia. These drugs include: Abilify, marketed by Bristol-Myers Squibb Company, Zyprexa, marketed by Eli Lilly, Vraylar, marketed by Allergan, Clozaril, marketed by Mylan Products Ltd., and Latuda, marketed by Sumitomo Dainippon Pharma Co., Ltd. Similarly, while there are currently no FDA-approved treatments for DRP, patients with Alzheimer's Disease, or AD, are prescribed drugs for enhancing their cognition, and include acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine and memantine. These medications are available generically although specific dosage forms and combinations are proprietary and marketed by large pharmaceutical companies such as Allergan, Janssen Pharmaceuticals NV, Novartis International AG and Pfizer Inc. Furthermore, patients with DRP may be prescribed antipsychotic medications that are indicated and approved for schizophrenia.

We believe that a significant number of product candidates are currently under development for the same indications we are currently pursuing, and may become commercially available in the future, for the treatment of conditions for which we may try to develop product candidates.

Our competitors may have significantly increased financial resources, a more established presence in the market and greater expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. Accordingly, our competitors may be more successful than we may be in obtaining regulatory approval for therapies and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our therapies obsolete or non-competitive before we can recover development and commercialization expenses. If KarXT is approved for the indications we are currently pursuing, it could compete with a range of therapeutic treatments that are in development. In addition, our competitors may succeed in developing, acquiring or licensing technologies and drug products that are more effective or less costly than KarXT or any other product candidates that we may develop, which could render our product candidates obsolete and noncompetitive.

If we obtain approval for KarXT or any other future product candidate, we may face competition based on many different factors, including the efficacy, safety and tolerability of our products, the ease with which our products can be administered, 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. Existing and future competing products could present superior treatment alternatives, including being more effective, safer, 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. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan.

In addition, our competitors may obtain patent protection, regulatory exclusivities or FDA approval and commercialize products more rapidly than we do, which may impact future approvals or sales of any of our product candidates that receive regulatory approval. If the FDA approves the commercial sale of KarXT or any other product candidate, we will also be competing with respect to marketing capabilities and manufacturing efficiency. We expect competition among products will be based on product efficacy and safety, the timing and scope of regulatory approvals, availability of supply, marketing and sales capabilities, product price, reimbursement coverage by government and private third-party payors, regulatory exclusivities and patent position. Our profitability and financial position will suffer if our product candidates receive regulatory approval but cannot compete effectively in the marketplace.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites, as well as in acquiring technologies complementary to, or necessary for, our programs.

KarXT is a patented combination of trospium, an FDA-approved generic drug, and xanomeline which exposes us to additional risks.

We are developing KarXT as a combination of trospium, which has been approved by the FDA for the treatment of overactive bladder, and xanomeline. Even if KarXT were to receive marketing approval or be commercialized, we would continue to be subject to the risks that the FDA or similar regulatory authorities could revoke approval of trospium or that safety, efficacy, manufacturing or supply issues could arise with trospium. This could result in our own products being removed from the market or being less commercially successful.

We may be unable to prevent third parties from selling, making, promoting, manufacturing, or distributing alternative combination therapies with xanomeline, or xanomeline as a single therapeutic.

We currently have two issued US patents directed to an oral medicament comprising certain doses of xanomeline and/or the salt thereof in combination with certain doses of trospium chloride, three issued US patents directed to methods for treating central nervous system disorders using combinations of certain oral doses of xanomeline and/or the salt thereof and certain oral doses of trospium chloride, as well as one issued US patent and one allowed US patent application directed to an oral pharmaceutical composition, comprising a plurality of xanomeline beads having a core comprising xanomeline or a salt thereof, and a plurality of trospium beads having a core comprising a salt of trospium. We also have one issued patent in Canada and one in Europe, with other patent applications pending in the US, Europe, Hong Kong, and Japan or awaiting nationalization from the PCT international stage. These patents would not prevent a third-party from creating, making, and marketing alternative combination therapies that fall outside the patent claim scope. There can be no assurance that any alternative combination therapies with xanomeline, or xanomeline as a single therapeutic, will not be therapeutically equivalent or commercially feasible. If an alternative combination with xanomeline, or xanomeline as a single therapeutic, is developed and approved for use in indications that we may seek approval for, the marketability and commercial success of KarXT, if approved, could be materially harmed.

If the FDA or comparable foreign regulatory authorities approve generic versions of KarXT or any other product candidate of ours that receives regulatory approval, or such authorities do not grant our products appropriate periods of non-patent exclusivity before approving generic versions of such products, the sales of such products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a “listed drug” in the FDA’s publication, “*Approved Drug Products with Therapeutic Equivalence Evaluations*,” or the Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration, conditions of use and labeling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning, in part, that it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Moreover, many states allow or require substitution of therapeutically equivalent generic drugs at the pharmacy level even if the branded drug is prescribed. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug may be lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the listed drug is invalid, unenforceable or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the listed drug. It is unclear whether the FDA will treat the xanomeline in our product candidates as an NCE and, therefore, afford them five years of NCE data exclusivity if approved. If any product we develop does not receive five years of NCE

exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Three-year exclusivity is given to a drug if it contains an active moiety that has previously been approved, and the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the NDA. If approved, manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products, if approved, may face from generic versions of our products could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

We currently have no commercial infrastructure. If we are unable to develop such infrastructure on our own or through collaborations with partners, we will not be successful in commercializing our product candidates.

We currently have no commercial infrastructure, which includes but is not limited to, marketing, sales or distribution capabilities. If KarXT is approved for the treatment of psychosis in patients with schizophrenia and DRP, we intend to establish a sales and marketing organization, either on our own or in collaboration with third parties, with technical expertise and supporting distribution capabilities to commercialize the approved product in key territories, which will require substantial additional resources. Some or all of these costs may be incurred in advance of any approval of KarXT. Any failure or delay in the development of our or third parties' internal sales, marketing and distribution capabilities would adversely impact the commercialization of KarXT and other future product candidates.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to our existing and future product candidates, we may choose to collaborate with third parties that have direct sales forces and established distribution systems to serve as an alternative to our own sales force and distribution systems. Our product revenue may be lower than if we directly marketed or sold our products, if approved. In addition, any revenue we receive will depend in whole or in part upon the efforts of these third parties, which may not be successful and are generally not within our control. If we are not successful in commercializing any approved products, our future product revenue will suffer and we may incur significant additional losses.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Any of our current and future product candidates for which we, or any future collaborators, obtain regulatory approval in the future will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. If approved, our product candidates could be subject to post-marketing restrictions or withdrawal from the market and we, or any future collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Any of our product candidates for which we, or any future collaborators, obtain regulatory approval, as well as the manufacturing processes, post-approval studies, labeling, advertising and promotional activities for such product, among other things, will be subject to ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. We and our contract manufacturers will also be subject to user fees and periodic inspection by the FDA and other regulatory authorities to monitor compliance with these requirements and the terms of any product approval we may obtain. Even if regulatory approval of a product candidate is granted, the approval may be subject to limitations on the indications or uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS.

The FDA and other regulatory authorities may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. If we, or any future collaborators, do not market any of our product candidates for which we, or they, receive regulatory approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing if it is alleged that we are doing so. Violation of the FDCA and other statutes relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws, including the False Claims Act.

In addition, later discovery of previously unknown adverse events or other problems with our products or their manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on the manufacturing of such products;
- restrictions on the labeling or marketing of such products;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- exclusion from federal health care programs such as Medicare and Medicaid;

- suspension or withdrawal of regulatory approvals;
- refusal to permit the import or export of products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Obtaining and maintaining marketing approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining marketing approval of our product candidates in other jurisdictions. Our failure to obtain regulatory approval in foreign jurisdictions would prevent our product candidates from being marketed abroad, and any approval we are granted for KarXT or any of our other product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding clinical trial design, safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approvals could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials which would be costly and time consuming and could delay or prevent introduction of KarXT or any of our other product candidates in those countries. We do not have experience in obtaining regulatory approval in international markets. If we or our partners fail to comply with regulatory requirements or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we, or any future collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations or third-party payor coverage and reimbursement policies, any of which could harm our business.

Patients who are provided medical treatment for their conditions generally rely on third party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any future collaborators to commercialize any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors including government health administration authorities and private health coverage insurers. Third-party payors decide which medications they will cover and establish reimbursement levels. We cannot be certain that coverage will be available and reimbursement will be adequate for KarXT for our initial or potential additional indications or for any other potential product candidates. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products.

If coverage and reimbursement are not available, or reimbursement is available only to limited levels, we, or any future collaborators, may be limited in our ability to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investment. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and 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.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Regulatory approvals, pricing and reimbursement for new drug products vary widely from country to country. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S.

Department of Health and Human Services, or HHS, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours. Reimbursement agencies in Europe may be more conservative than CMS, but ultimately make their own coverage determinations. Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these foreign jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for certain medications, which could affect our ability or that of any future collaborators to sell our product candidates profitably. For example, the Trump administration previously released a “Blueprint” to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out-of-pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for prior authorization, Part B drugs beginning January 1, 2020. This final rule codified CMS’s policy change that was effective January 1, 2019.

In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. Some of these changes are undergoing legal challenges, and their status is currently in question. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress has indicated that it may continue to seek new legislative and/or administrative measures to control drug costs.

At the state level, legislatures are increasingly 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. Payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any future collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any future collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging prices. We cannot be sure that coverage will be available for any product candidate that we, or any future collaborator, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from one country to another. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any future collaborator, obtain regulatory approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

We may seek Breakthrough Therapy Designation by the FDA for a product candidate that we develop, and we may be unsuccessful. If we are successful, the designation may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek Breakthrough Therapy Designation for any product candidate that we develop. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval and priority review.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe a product candidate we develop meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if the product candidates we develop qualify as breakthrough therapies, the FDA may later decide that the drugs no longer meet the conditions for qualification and rescind the designation.

We may seek Fast Track Designation by the FDA for a product candidate that we develop, and we may be unsuccessful. If we are successful, the designation may not actually lead to a faster development or regulatory review or approval process.

We may seek Fast Track Designation for the product candidates we develop. If a product is intended for the treatment of a serious or life-threatening condition and preclinical or clinical data demonstrate the potential to address an unmet medical need for this condition, the product sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may rescind the Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

Product liability lawsuits against us or any of our future collaborators could divert our resources and attention, cause us to incur substantial liabilities and limit commercialization of our product candidates.

We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of pharmaceutical products. Currently, we have no products that have been approved for commercial sale; however, the use of our product candidates by us and any collaborators in clinical trials, and the sale of these product candidates, if approved, in the future, may expose us to liability claims. We face an inherent risk of product liability lawsuits related to the use of our product candidates in elderly patients and will face an even greater risk if product candidates are approved by regulatory authorities and introduced commercially. Product liability claims may be brought against us or our partners by participants enrolled in our clinical trials, patients, health care providers, pharmaceutical companies, our collaborators or others using, administering or selling any of our future approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any of our future approved products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- significant litigation costs;
- substantial monetary awards to, or costly settlements with, patients or other claimants;
- product recalls or a change in the indications for which they may be used;
- loss of revenue;
- diversion of management and scientific resources from our business operations; and
- the inability to commercialize our product candidates.

Although the clinical trial process is designed to identify and assess potential side effects, clinical development does not always fully characterize the safety and efficacy profile of a new medicine, and it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If our product candidates were to cause adverse side effects during clinical trials or after approval, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates. If any of our product candidates are approved for commercial sale, we will be highly dependent upon consumer perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity associated with illness or other adverse effects resulting from patients' use or misuse of our products or any similar products distributed by other companies.

Although we maintain product liability insurance coverage in the amount of up to $10.0 million in the aggregate, including clinical trial liability, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if we commercialize any product that receives regulatory approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

Even if we, or any future collaborators, obtain regulatory approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products, which could impair our ability to generate revenue.

Once regulatory approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We, and any future collaborators, must therefore comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain regulatory approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we and any future collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practices, or cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, any future collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs. Despite our efforts to inspect and verify regulatory compliance, one or more of our third-party manufacturing vendors may be found on regulatory inspection by FDA or other authorities to be not in compliance with cGMP regulations, which may result in shutdown of the third-party vendor or invalidation of drug product lots or processes. In some cases, a product recall may be warranted or required, which would materially affect our ability to supply and market our drug products.

Accordingly, assuming we, or any future collaborators, receive regulatory approval for one or more of our product candidates, we, and any future collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

If we, and any future collaborators, are not able to comply with post-approval regulatory requirements, we, and any future collaborators, could have the regulatory approvals for our products withdrawn by regulatory authorities and our, or any future collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, privacy and transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we obtain regulatory approval. Our arrangements with third party payors, healthcare providers and physicians may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any products for which we obtain regulatory approval. These include the following:

- **Anti-Kickback Statute**—The federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers, among others, on the other. A person or entity can be found guilty of violating the federal Anti-Kickback Statute without actual

knowledge of the statute or specific intent to violate it. 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 federal civil False Claims Act or federal civil money penalties statute;

- **Federal civil and criminal false claims laws and civil monetary penalty laws, including False Claims Laws**—The federal civil and criminal false claims laws, including the federal civil False Claims Act, and federal civil monetary penalties laws which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent; knowingly making or causing a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government A claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim under the federal civil False Claims Act. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a "whistleblower" to bring *qui tam* actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- **HIPAA**—The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, 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 attorneys' fees and costs associated with pursuing federal civil actions;
- **Transparency Requirements**—The federal Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the HHS under the Open Payments Program, information related to payments or other transfers of value made to physicians, certain other healthcare professionals, and teaching hospitals, as well as ownership and investment interests held by physicians, certain other healthcare professional and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners; and
- **Analogous State and Foreign Laws**—Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, which may be broader in scope and apply regardless of payor. These laws are enforced by various state agencies and through private actions. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant federal government compliance guidance, require drug manufacturers to report information related to payments and other transfers of value to

physicians and other healthcare providers, and restrict marketing practices or require disclosure of marketing expenditures or drug pricing. Some state and local laws require the registration of pharmaceutical sales representatives. State and foreign laws also govern the privacy and security of health information in some circumstances. These data privacy and security laws may differ from each other in significant ways and often are not pre-empted by HIPAA, which may complicate compliance efforts.

In addition to the above, on November 20, 2020, the Office of Inspector General, or OIG, finalized further modifications to the federal Anti-Kickback Statute. Under the final rules, OIG added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others. The final rule (with some exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business.

Efforts to ensure that our business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, 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 these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity and oversight agreements to resolve allegations of non-compliance, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Defending against any such actions can be costly and 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 healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is generally not permitted in the countries that form part of the European Union. Some European Union Member States, like the United Kingdom, through the United Kingdom Bribery Act 2010, have enacted laws explicitly prohibiting the provision of these types of benefits and advantages. Infringements of these laws can result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States (e.g., France or Belgium) must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the European Union Member State national laws, industry codes (e.g. the European Federation of Pharmaceutical Industries and Associations Disclosure and Healthcare Professionals Codes) or professional codes of conduct. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

The collection and processing of personal data—including health data—is governed by the European Union-wide General Data Protection Regulation, or GDPR, which became applicable on May 25, 2018, replacing the current data protection laws of each European Union Member State. GDPR applies to any business, regardless of its location, that provides goods or services to residents in the EU. This expansion includes our clinical trial activities in European Union Member States. The GDPR imposes more stringent operational requirements for processors and controllers of personal data, including, for example, special protections for "sensitive information" which includes health and genetic information of data subjects residing in the EU, expanded disclosures about how personal information is to be used, limitations on retention of information, increased requirements pertaining to health data and pseudonymised (i.e., key-coded) data,

mandatory data breach notification requirements and higher standards for controllers to demonstrate that they have obtained valid consent for certain data processing activities. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedies in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the European Union to the United States or other regions that have not been deemed to offer "adequate" privacy protections. The GDPR provides that European Union Member States may make their own further laws and regulations in relation to the processing of genetic, biometric or health data, which could result in differences between Member States, limit our ability to use and share personal data or could cause our costs to increase, and harm our business and financial condition. We are also subject to evolving and strict rules on the transfer of personal data out of the European Union to the United States. Failure to comply with European Union data protection laws may result in fines (for example, of up to €20,000,000 or up to 4% of the total worldwide annual turnover of the preceding financial year (whichever is higher) under the GDPR) and other administrative penalties, which may be onerous and adversely affect our business, financial condition, results of operations and prospects. As a result of the implementation of the GDPR, we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. There is significant uncertainty related to the manner in which data protection authorities will seek to enforce compliance with GDPR is not yet clear. For example, it is not clear if the authorities will conduct random audits of companies doing business in the EU, or if the authorities will wait for complaints to be filed by individuals who claim their rights have been violated. Enforcement uncertainty and the costs associated with ensuring GDPR compliance be onerous and adversely affect our business, financial condition, results of operations and prospects.

Current and future legislation may increase the difficulty and cost for us and any collaborators to obtain regulatory approval of and commercialize our product candidates and affect the prices we, or they, may obtain.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay regulatory approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain regulatory approval. We expect that current laws, as well as 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 in additional downward pressure on the price that we, or any collaborators, may receive for any approved products.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA. Among the provisions of the ACA of potential importance to our business and our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription products and biologic products;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts, which was increased to 70% by the Bipartisan Budget Act of 2018, off negotiated prices of applicable brand products to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient products to be covered under Medicare Part D;

- extension of manufacturers' Medicaid rebate liability to individuals enrolled in Medicaid managed care organizations;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report product samples that manufacturers and distributors provide to physicians;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models.

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. Since January 2017, President Trump has signed two executive orders and other directives designed to delay the implementation of certain provisions of 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, it has enacted laws that modify certain provisions of the ACA. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision that repealed, 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 Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. Pending review, the ACA remains in effect, but it is unclear at this time what effect the latest ruling will have on the status of the ACA.

On January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. On June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. This was appealed to the U.S. Supreme Court, which heard arguments on December 10, 2019. The United States Supreme Court is expected to rule on the legal challenge to the constitutionality of the ACA in early 2021. We cannot predict how the U.S. Supreme Court will rule. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. In December 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. On January 31, 2020, CMS issued the proposed annual Notice of Benefit and Payment Parameters Rule for 2021, which, in part, sets the parameters for the risk adjustment program. In addition, CMS published a final rule that would give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

Moreover, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. However, on December 20, 2019, President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future. The Bipartisan Budget Act of 2018, also amended the ACA, effective January 1, 2019, by increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and closing the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In December 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On January 31, 2020, CMS issued the proposed annual Notice of Benefit and Payment Parameters Rule for 2021, which, in part, will set the parameters for the risk adjustment program. In addition, CMS has published a final rule that would give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2029 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws and regulations may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

There has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal years 2019 and 2020 contain further drug price control measures that could be enacted during the budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. The Trump administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions.

Additionally, the Trump administration previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs, effective January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative

measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing Reduction Act of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. An even more restrictive bill, the Lower Drug Costs Now Act of 2019, was introduced in the House of Representatives on September 19, 2019, passed the House on December 12, 2019, and was received in the Senate four days later. This bill, if passed, would require the HHS to directly negotiate drug prices with manufacturers. It is unclear whether either of these bills will be signed into law, and if either is enacted, what effect it would have on our business.

Further, on July 24, 2020 and September 13, 2020, President Trump signed a series of Executive Orders aimed at lowering drug prices and at implementing several of the administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all U.S. states and territories for a seven-year period beginning January 1, 2021 and ending December 31, 2027. The Interim Final Rule has not been finalized and is subject to revision and challenge. Additionally, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

In addition, individual states have also become increasingly active in passing legislation and implementing 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, to encourage importation from other countries and bulk purchasing.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at containing or lowering the cost of healthcare. 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. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if approved;
- our ability to receive or set a price that we believe is fair for our products;

- our ability to generate revenue and achieve or maintain profitability;
- the amount of taxes that we are required to pay; and
- the availability of capital.

We expect that the ACA, as well as 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, lower reimbursement, and new payment methodologies. This could lower the price that we receive for any approved product. Any denial in coverage or reduction in reimbursement from Medicare or other government-funded programs may result in a similar denial or reduction in payments from private payors, which may prevent us from being able to generate sufficient revenue, attain profitability or commercialize our product candidates, if approved.

Governments outside the United States may impose strict price controls, which may adversely affect our revenues, if any.

In some countries, including Member States of the European Union, the pricing of prescription drugs is subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. In some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of any of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time-consuming and costly. We cannot be sure that such prices and reimbursement will be acceptable to us or our strategic partners. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our strategic partners and the potential profitability of any of our product candidates in those countries would be negatively affected.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the United States and require us to develop and implement costly compliance programs.

We must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate outside the United States, including those countries outside the United States in which we plan to conduct clinical trials as part of our EMERGENT program. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders, including export control and trade sanctions laws, also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Environmental laws and regulations may impair our research, development or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Risks Related to Our Dependence on Third Parties

We may seek to establish collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

The advancement of our product candidates and development programs and the potential commercialization of our current and future product candidates will require substantial additional cash to fund expenses. For some of our programs, we may decide to collaborate with additional pharmaceutical and biotechnology companies with respect to development and potential commercialization. Likely collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if we are able to obtain regulatory approval for product candidates from foreign regulatory authorities, we may enter into collaborations with international biotechnology or pharmaceutical companies for the commercialization of such product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidate from competing product candidates, design or results of clinical trials, the likelihood of

approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Collaborations are complex and time-consuming to negotiate and document. Further, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Any collaboration agreements that we enter into in the future may contain restrictions on our ability to enter into potential collaborations or to otherwise develop specified product candidates. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

If we enter into collaborations with third parties for the development and commercialization of our product candidates, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We may enter into collaborations for the development and commercialization of certain of our product candidates. If we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on any future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, including trade secrets and intellectual property rights, contract interpretation, or the preferred course of development might cause delays or termination of the research, development or commercialization of product

candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any future collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed to it by us.

We rely on third parties to assist in conducting our clinical trials. If they do not perform satisfactorily, we may not be able to obtain regulatory approval or commercialize our product candidates, or such approval or commercialization may be delayed, and our business could be substantially harmed.

We have relied upon and plan to continue to rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials and expect to rely on these third parties to conduct clinical trials of any other product candidate that we develop. Any of these third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which could negatively impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects.

Further, although our reliance on these third parties for clinical development activities limits our control over these activities, we remain responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards. Moreover, the FDA requires us to comply with Good Clinical Practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The FDA enforces these GCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites and IRBs. If we or our third-party contractors fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our product candidates, which would delay the regulatory approval process. We cannot be certain that, upon inspection, the FDA will determine that any of our clinical trials comply with GCPs. We are also required to register certain clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, the third parties conducting clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time, skill and resources to our ongoing development programs. These contractors 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, which could impede their ability to devote appropriate time to our clinical programs. If these third parties, including clinical investigators, do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we may not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. In such an event, our financial results and the commercial prospects for any product candidates that we seek to develop could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or regulatory approval of our product candidates or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue.

Our use of third parties to manufacture our product candidates may increase the risk that we will not have sufficient quantities of our product candidates, products, or necessary quantities of such materials on time or at an acceptable cost.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely on third parties for the manufacture and supply of the active pharmaceutical ingredients, or APIs, in our product candidates. Our current strategy is to outsource all manufacturing of our product candidates to third parties.

We currently engage third-party manufacturers to provide the APIs of KarXT and for the final drug product formulation of KarXT that is being used in our clinical trials. Although we believe that there are several potential alternative manufacturers who could manufacture KarXT, we may incur added costs and delays in identifying and qualifying any such replacement. In addition, we typically order raw materials and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements with any commercial manufacturer. There is no assurance that we will be able to timely secure needed supply arrangements on satisfactory terms, or at all. Our failure to secure these arrangements as needed could have a material adverse effect on our ability to complete the development of our product candidates or to commercialize them, if approved. We may be unable to conclude agreements for commercial supply with third-party manufacturers, or may be unable to do so on acceptable terms. There may be difficulties in scaling up to commercial quantities and formulation of KarXT, and the costs of manufacturing could be prohibitive.

Even if we are able to establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the failure of the third-party manufacturer to comply with applicable regulatory requirements and reliance on third-parties for manufacturing process development, regulatory compliance and quality assurance;
- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- limitations on supply availability resulting from capacity and scheduling constraints of third-parties or the impacts of the COVID-19 pandemic;
- the possible breach of manufacturing agreements by third-parties because of factors beyond our control;
- the possible termination or non-renewal of the manufacturing agreements by the third-party, at a time that is costly or inconvenient to us; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

If we do not maintain our key manufacturing relationships, we may fail to find replacement manufacturers or develop our own manufacturing capabilities, which could delay or impair our ability to obtain regulatory approval for our products. If we do find replacement manufacturers, we may not be able to enter into agreements with them on terms and conditions favorable to us and there could be a substantial delay before new facilities could be qualified and registered with the FDA and other foreign regulatory authorities.

Our third-party manufacturers may be subject to damage or interruption from, among other things, fire, natural or man-made disaster, the COVID-19 pandemic, power loss, telecommunications failure, unauthorized entry, computer viruses, denial-of-service attacks, acts of terrorism, human error, vandalism or sabotage, financial insolvency, bankruptcy and similar events.

If KarXT for any of our initial or potential additional indications or any other product candidate is approved by any regulatory agency, we intend to utilize arrangements with third-party contract manufacturers for the commercial production of those products. This process is difficult and time consuming and we may face competition for access to manufacturing facilities as there are a limited number of contract manufacturers operating under cGMPs that are capable of manufacturing our product candidates. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, which could delay our commercialization.

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 voluntary recalls of product candidates, operating restrictions and criminal prosecutions, any of which could significantly affect supplies of our product candidates. The facilities used by our contract manufacturers to manufacture our product candidates must be evaluated by the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMPs. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we may not be able to secure and/or maintain regulatory approval for our product manufactured at these facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA finds deficiencies 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. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. Any failure to comply with cGMP requirements or other FDA, EMA and comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop our product candidates and market our products, if approved.

The FDA and other foreign regulatory authorities require manufacturers to register manufacturing facilities. The FDA and corresponding foreign regulators also inspect these facilities to confirm compliance with cGMPs. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. Any failure to comply with cGMP requirements or other FDA, EMA and comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop our product candidates and market our products following approval.

If any third-party manufacturer of our product candidates is unable to increase the scale of its production of our product candidates, and/or increase the product yield of its manufacturing, then our costs to manufacture the product may increase and commercialization may be delayed.

In order to produce sufficient quantities to meet the demand for clinical trials and, if approved, subsequent commercialization of KarXT, or any other product candidates that we may develop, our third-party manufacturers will be required to increase their production and optimize their manufacturing processes while maintaining the quality of the product. The transition to larger scale production could prove difficult. In addition, if our third party manufacturers are not able to optimize their manufacturing processes to increase the product yield for our product candidates, or if they are unable to produce increased amounts of our product candidates while maintaining the quality of the product, then we may not be able to meet the demands of clinical trials or market demands, which could decrease our ability to generate profits and have a material adverse impact on our business and results of operation.

We may need to maintain licenses for active ingredients from third parties to develop and commercialize some of our product candidates, which could increase our development costs and delay our ability to commercialize those product candidates.

Should we decide to use API in any of our product candidates that are proprietary to one or more third parties, we would need to maintain licenses to those active ingredients from those third parties. If we are unable to gain or continue to access rights to these active ingredients prior to conducting preclinical toxicology studies intended to support clinical trials, we may need to develop alternate product candidates from these programs by either accessing or developing alternate active ingredients, resulting in increased development costs and delays in commercialization of these product candidates. If we are unable to gain or maintain continued access rights to the desired active ingredients on commercially reasonable terms or develop suitable alternate active ingredients, we may not be able to commercialize product candidates from these programs.

Use of third parties to conduct testing of our product candidates in tissues or animals may increase the risk that we will have unsuitable or invalidated data for regulatory submissions and approval.

We currently do not own or operate laboratory facilities in which to conduct preclinical testing of our product candidates in tissues or animals. Preclinical studies regulated by FDA, EMA and most other health authorities are governed by Good Laboratory Practices, or GLP. Additionally, studies involving animals may be subject to further regulation by institutional, private or government animal welfare authorities that may vary by territory. Studies involving human tissues may also be subject to institutional and government human subject privacy policies that may vary by territory. Third party vendors conducting tissue and/or animal studies on our behalf may be found to be in violation of one or more of these regulations or policies and may be subject to closure, censure or other penalties. In some cases, these penalties could materially impact the performance, availability, or validity of studies conducted on our behalf. Even in the absence of violations resulting in penalties, regulatory and other authorities may refuse to authorize the conduct or to accept the results of studies for regulatory or ethical reasons.

Risks Related to Our Intellectual Property

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

Our commercial success depends in large part on our ability to obtain and maintain intellectual property rights protection through patents, trademarks, and trade secrets in the United States and other countries with respect to our proprietary product candidates. If we do not adequately protect our intellectual property rights, competitors may be able to erode, negate or preempt any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we have patent applications and may file other patent applications in the United States or abroad related to our product candidates that are important to our business; we may also license or purchase patent applications filed by others. The patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented, how claims are amended, and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. We may not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we may license in the future, and therefore cannot guarantee that these patents and applications will be prosecuted or maintained in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensor or future licensor have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents.

If the scope of the patent protection we or our future licensors obtain is not sufficiently broad, we may not be able to prevent others from developing and commercializing technology and products similar or identical to ours. The degree of patent protection we require to successfully compete in the marketplace may be

unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our licensed patents have, or that any of our pending owned or licensed patent applications that mature into issued patents will include, claims with a scope sufficient to protect our proprietary platform or otherwise provide any competitive advantage, nor can we assure you that our licenses are or will remain in force. Other parties have developed or may develop technologies that may be related or competitive with our approach, and may have filed or may file patent applications and may have been issued or may be issued patents with claims that overlap or conflict with our patent applications, either by claiming the same compounds, formulations or methods or by claiming subject matter that could dominate our patent position. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally twenty years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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 adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates.

Even if they are unchallenged, our owned and licensed patent and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, a third party may develop a competitive therapy that provides benefits similar to our product candidate but falls outside the scope of our patent protection or license rights. If the patent protection provided by the patent and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidate could be negatively affected, which would harm our business. Currently, a significant portion of our patents and patent applications are in-licensed, though similar risks would apply to any patents or patent applications that we now own or may own or in-license in the future.

We, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to strengthen our patent position.

It is possible that defects of form in the preparation or filing of our patent or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees, or licensors, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent position of biotechnology and pharmaceutical companies carries uncertainty. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which are dependent upon the current legal and intellectual property context, extant legal precedent and interpretations of the law by individuals. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are characterized by uncertainty.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are not published until 18 months after filing, or in some cases not at all.

Therefore, we cannot be certain that we were the first to make the inventions claimed in our patent or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed prior patent applications on inventions claimed in our patents or applications that were filed on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such prior applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or to other patent offices around the world. Alternately or additionally, we may become involved in post-grant review procedures, oppositions, derivation proceedings, *ex parte* reexaminations, *inter partes* review, supplemental examinations, or interference proceedings or challenges in district court, in the United States or in various foreign patent offices, including both national and regional, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenges may result in loss of the patent or in patent or patent application claims being narrowed, invalidated or held unenforceable, in whole or in part, or in denial of the patent application or loss or reduction in the scope of one or more claims of the patent or patent application, any of 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 technology and products. In addition, 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.

Pending and future patent applications may not result in patents being issued that protect our business, in whole or in part, or which effectively prevent others from commercializing competitive products. Competitors may also be able to design around our patents. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, patent laws in various jurisdictions, including significant commercial markets such as Europe, restrict the patentability of methods of treatment of the human body more than United States law does. If these developments were to occur, they could have a material adverse effect on our ability to generate revenue.

The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting our product candidates by obtaining and defending patents. These risks and uncertainties include 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. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case;
- patent applications may not result in any patents being issued;

- patents that may be issued or in-licensed 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 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 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.

Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

In addition, we rely on the protection of our trade secrets and proprietary, unpatented know-how. 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 invention assignment agreements with employees, consultants, collaborators, vendors, and advisors, we cannot provide any assurances that all such agreements have been duly executed, and third parties may still obtain this information or may come upon this or similar information independently. It is possible that technology relevant to our business will be independently developed by a person who is not a party to such a confidentiality or invention assignment agreement. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, collaborators, vendors, advisors, former employees and current employees. Furthermore, if the parties to our confidentiality agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a consequence of such breaches or violations. Our trade secrets could otherwise become known or be independently discovered by our competitors. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets. If any of these events occurs or if we otherwise lose protection for our trade secrets or proprietary know-how, our business may be harmed.

If we fail to comply with our obligations in our current and future intellectual property licenses with third parties, we could lose rights that are important to our business.

We are party to a patent license agreement with PureTech Health that provides us with intellectual property rights relating to KarXT. This license agreement imposes milestone payment, royalty and other obligations on us. If we fail to comply with our obligations, including achieving specified milestone events, PureTech Health may have the right to terminate this license, in which event we might not be able to develop, manufacture or market any product that is covered by the intellectual property we in-license from PureTech Health and may face other penalties. Such an occurrence would materially adversely affect our business prospects. For a variety of purposes, we will likely enter into additional licensing and funding arrangements with third parties that may also impose similar obligations on us.

Termination of any of our current or future in-licenses would reduce or eliminate our rights under these agreements and may result in our having to negotiate new or reinstated agreements with less favorable terms or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology. Any of the foregoing could prevent us from commercializing our product candidate, which could have a material adverse effect on our operating results and overall financial condition.

In addition to the above risks, intellectual property rights that we license in the future may include sublicenses under intellectual property owned by third parties, in some cases through multiple tiers. The actions of our future licensors may therefore affect our rights to use our sublicensed intellectual property, even if we are in compliance with all of the obligations under our license agreements. Should our licensor or any of the upstream licensors fail to comply with their obligations under the agreements pursuant to which they obtain the rights that are sublicensed to us, or should such agreements be terminated or amended, our ability to develop and commercialize our product candidates may be materially harmed.

Moreover, disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our product candidates, technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

It is difficult and costly to protect our intellectual property and our proprietary technologies, and we may not be able to ensure their protection.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection for the use, formulation and structure of our product candidate, and associated methods of treatment as well as on successfully defending these patents against potential third-party challenges. Our ability to protect our product candidate from unauthorized making, using, selling, offering to sell or importing by third parties is dependent on the extent to which we have rights under valid and enforceable patents that cover these activities.

The patent positions of pharmaceutical, biotechnology and other life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved and have in recent years been the subject of much litigation. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Further, the determination that a patent application or patent claim meets all of the requirements for patentability is a subjective determination based on the application of law and jurisprudence.

The ultimate determination by the USPTO or by a court or other trier of fact in the United States, or corresponding foreign national patent offices or courts, on whether a claim meets all requirements of patentability cannot be assured. Although we have conducted searches for third-party publications, patents and other information that may affect the patentability of claims in our various patent applications and patents, we cannot be certain that all relevant information has been identified. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our owned patents or patent applications, in our licensed patents or patent applications or in third-party patents.

We cannot provide assurances that any of our patent applications will be found to be patentable, including over our own or our licensors' prior art publications or patent literature, or will issue as patents. Neither can we make assurances as to the scope of any claims that may issue from our pending and future patent applications nor to the outcome of any proceedings by any potential third parties that could challenge the patentability, validity or enforceability of our patents and patent applications in the United States or foreign jurisdictions. Any such challenge, if successful, could limit patent protection for our products and product candidates and/or materially harm our business.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- we may not be able to generate sufficient data to support full patent applications that protect the entire breadth of developments in one or more of our programs;
- it is possible that one or more of our pending patent applications will not become an issued patent or, if issued, that the patent(s) claims will have sufficient scope to protect our technology, provide us with a basis for commercially viable products or provide us with any competitive advantages;
- if our pending applications issue as patents, they may be challenged by third parties as not infringed, invalid or unenforceable under United States or foreign laws;
- if issued, the patents under which we hold rights may not be valid or enforceable;
- we may not successfully commercialize KarXT, if approved, before our relevant patents expire;
- we may not be the first to make the inventions covered by each of our patents and pending patent applications; or
- we may not develop additional proprietary technologies or product candidates that are separately patentable.

In addition, to the extent that we are unable to obtain and maintain patent protection for one of our products or product candidates or in the event that such patent protection expires, it may no longer be cost-effective to extend our portfolio by pursuing additional development of a product or product candidate for follow-on indications.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.

In addition to patents, we also may rely on trade secrets to protect our technologies or products, especially where we do not believe patent protection is appropriate or obtainable. Also, we cannot provide any assurances that any of our licensed patents have claims with a scope sufficient to protect our technology or otherwise provide any competitive advantage, nor can we assure you that our licenses are or will remain in full force or effect, in which case we would similarly rely on trade secrets. However, trade secrets are difficult to protect. We seek to protect our confidential proprietary information, in part, by confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and collaborators. These agreements are designed to protect our proprietary information. However, we cannot be certain that such agreements have been entered into with all relevant parties, and we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not

otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. For example, our employees, consultants, contractors, outside scientific collaborators and other advisers may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third-party entity illegally obtained and is using any of our trade secrets is expensive and time-consuming, and the outcome is unpredictable, and we may not be able to obtain adequate remedies for such breaches. We also seek to preserve the integrity and confidentiality of our confidential proprietary information by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Notably, proprietary technology protected by a trade secret does not preempt the patenting of independently developed equivalent technology, even if such equivalent technology is invented subsequent to the technology protected by a trade secret. If any of our confidential proprietary information were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance 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. In such a circumstance, competitors may be able to enter the market earlier than otherwise would be the case. Under the terms of some of our current and future licenses, we may not have the ability to maintain patents or prosecute patent applications in the portfolio, and may therefore have to rely on third parties to comply with these requirements.

Patent terms may be inadequate to protect our competitive position on our products 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 non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. 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. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to seven and a half years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). We might not be granted an extension because of, for example, failure to apply within applicable periods, failure to apply prior to the expiration of relevant patents or otherwise failure to satisfy any of the numerous applicable requirements. Moreover, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to obtain approval of competing products following our patent expiration by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. If this were to occur, it could have a material adverse effect on our ability to generate revenue.

Changes to patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our commercial success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Wide-ranging patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system, expanding the definition of prior art, and developing a post-grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post-grant review and *inter partes* review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent filed March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for *inter partes* review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for *inter partes* review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas *inter partes* review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts, and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U.S. patent invalidated in a USPTO post-grant review or *inter partes* review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which may result in a loss of the challenged patent right to us.

In addition, recent court rulings in cases such as *Association for Molecular Pathology v. Myriad Genetics, Inc., BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation, and Promega Corp. v. Life Technologies Corp.* have narrowed the scope of patent protection available in certain circumstances and weakened 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 future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, 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 that we might obtain in the future.

We may not be able to enforce our intellectual property rights throughout the world.

Filing, prosecuting, enforcing and defending patents on our product candidate 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. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to

stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe or from selling or importing products made from 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 and market their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of such enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings 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. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products, if approved. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Others may challenge inventorship or claim an ownership interest in our intellectual property which could expose it to litigation and have a significant adverse effect on its prospects.

A third party or former employee or collaborator may claim an inventorship or ownership interest in one or more of our or our licensors' patents or other proprietary or intellectual property rights. A third party could bring legal actions against us and seek monetary damages and/or enjoin clinical testing, manufacturing and marketing of the affected product or products. While we are presently unaware of any claims or assertions by third-parties with respect to our patents or other intellectual property, we cannot guarantee that a third party will not assert a claim or an interest in any of such patents or intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Further, regardless of the outcome, if we become involved in any litigation, it could consume a substantial portion of our resources, and cause a significant diversion of effort by our technical and management personnel.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidate without infringing the intellectual property and other 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. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds, methods of manufacturing compounds and/or methods of use for the treatment of the disease indications for which we are developing our product candidates. If any third-party patents or patent applications are found to cover our product candidates or their methods of use or manufacture, we may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our products candidates, including patent infringement lawsuits in the US or abroad, as well as interference, derivation, *inter partes* review, and post-grant proceedings before the USPTO and opposition or other proceedings before corresponding foreign patent offices. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the composition, use or manufacture of our product candidates. We cannot guarantee that any of our patent searches or analyses including, but not limited to, the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on intellectual property rights that exist now or arise in the future. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use or manufacture. The scope of protection afforded by a patent is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, 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, and we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. If we were required to obtain a license to continue to manufacture or market the affected product, we may be required to pay substantial royalties or grant cross-licenses to our patents. We cannot, however, assure you that any such license will be available on acceptable terms, if at all. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations as a result of claims of patent infringement or violation of other intellectual property rights, Further, the outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance, including the demeanor and credibility of witnesses and the identity of any adverse party. This is especially true in intellectual property cases that may turn on the testimony of experts as to technical facts upon which experts may reasonably disagree. Furthermore, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us; alternatively or additionally it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. 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 subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our current and former employees and our licensors' current and former employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, including some which may be competitors or potential competitors. Some of these employees, including members of our senior management, may have executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may sustain damages or lose key personnel, valuable intellectual property rights or the personnel's work product, which could hamper or prevent commercialization of our technology, which could materially affect our commercial development efforts. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

We may become involved in lawsuits to protect or enforce our patent or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patent, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patent could limit our ability to assert those patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the trademarks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for

years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Additionally, for certain of our existing and future in-licensed patent rights, we may not have the right to bring suit for infringement and may have to rely on third parties to enforce these rights for us. If we cannot or choose not to take action against those we believe infringe our intellectual property rights, we may have difficulty competing in certain markets where such potential infringers conduct their business, and our commercialization efforts may suffer as a result.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our trademarks of interest and our business may be adversely affected.

Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We rely on both registration and common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Moreover, any name we propose to use for our products in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed product names, we may be required to expend significant additional resources in an effort to identify a usable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Employee Matters and Managing Growth

We depend heavily on our executive officers, principal consultants and others, and the loss of their services would materially harm our business.

Our success depends, and will likely continue to depend, upon our ability to hire, retain the services of our current executive officers, principal consultants and others, including Steven Paul, our President and Chief Executive Officer, Andrew Miller, our Chief Operating Officer, Stephen Brannan, our Chief Medical Officer, and Troy Ignelzi, our Chief Financial Officer. We have entered into employment agreements with Dr. Paul, Dr. Miller, Dr. Brannan and Mr. Ignelzi, but they may terminate their employment with us at any time. The loss of their services might impede the achievement of our research, development and commercialization objectives.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. Our industry has experienced a high rate of turnover of management personnel in recent years. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully.

Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key employees on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions.

We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited.

We only have a limited number of employees to manage and operate our business.

As of February 15, 2021, we had 63 full-time employees. Our focus on the development of KarXT requires us to optimize cash utilization and to manage and operate our business in a highly efficient manner. We cannot assure you that we will be able to hire and/or retain adequate staffing levels to develop KarXT or run our operations and/or to accomplish all of the objectives that we otherwise would seek to accomplish.

Our employees, independent contractors, consultants, collaborators and contract research organizations may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates:

- FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities;
- manufacturing standards;
- federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities; and
- laws that require the reporting of financial information or data accurately.

Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of product materials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, 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, standards or regulations. Additionally, 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 results of operations, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, disgorgement, integrity oversight and reporting obligations, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations.

We expect to expand our organization and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of regulatory affairs and sales, marketing and distribution, as well as to support our public company operations. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to

effectively manage the expansion of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates.

Risks Related to Our Common Stock

An active trading market for our common stock may not be sustainable, investors may not be able to resell their shares at or above the purchase price and our ability to raise capital in the future may be impaired.

In June 2019, we closed our initial public offering. Prior to our initial public offering, there was no public market for our common stock. Although we completed our initial and follow-on public offerings and shares of our common stock are listed on The Nasdaq Global Market, an active trading market for our shares may not be maintained. If an active market for our common stock is not maintained, it may be difficult for our investors to resell their shares without depressing the market price for the shares or at all. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

The trading price of our common stock is likely to continue to be highly volatile. Securities class action or other litigation involving our company or members of our management team could also substantially harm our business, financial condition and results of operations.

Our stock price is volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- the success of existing or new competitive products or technologies;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of KarXT and any other product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;

- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

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 biopharmaceutical companies, which have experienced significant stock price volatility in recent years.

If securities analysts publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock depends in part on the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us issues an adverse opinion about our company, our stock price would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

As of January 1, 2021, we are no longer an “emerging growth company” or a “smaller reporting company,” and the reduced disclosure requirements applicable to emerging growth and smaller reporting companies no longer apply to us.

As of June 30, 2020, the market value of our common stock that was held by non-affiliates exceeded $700 million and, as a result, as of January 1, 2021 we no longer qualified as an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or a “smaller reporting company.” As a large accelerated filer, we are subject to certain disclosure requirements that are applicable to other public companies that were not applicable to us as an emerging growth company. These requirements include:

- compliance with the auditor attestation requirements in the assessment of our internal control over financial reporting imposed by Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404;
- compliance 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; and
- full disclosure obligations regarding executive compensation.

In addition, we are no longer able to take advantage of transition periods for complying with new or revised accounting standards that are available to emerging growth companies.

We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, particularly now that we are no longer an “emerging growth company,” we have incurred, and will continue to incur, significant legal, accounting and other expenses that we did not incur as a private company, including costs associated with public company reporting requirements. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. Because we are no longer an emerging growth company, we are required to include with this annual report an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have been and will continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting.

Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404 or that we will not be able to comply with the requirements of Section 404 in a timely manner. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements. If this were to occur, we could also be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal control over financial reporting from our independent registered public accounting firm.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared nor paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. In addition, the terms of any future debt or credit agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Based upon 27,018,734 shares outstanding as of February 15, 2021, our executive officers and directors, combined with our stockholders who own more than 5% of our outstanding common stock and their affiliates, in the aggregate, beneficially own shares representing approximately 55.8% of our common stock. If our stockholders who own more than 5% of our outstanding common stock were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they chose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management or the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the price at which shares were sold in our public offerings and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other stockholders.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our consolidated financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. Additionally, no that we are no longer an "emerging growth company" under the JOBS Act, our independent registered public accounting firm is required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Upon the closing of our initial public offering in July 2019, we became subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions 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, employees or agents.

Our restated certificate of incorporation specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving state law claims brought against us by stockholders. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our restated certificate of incorporation described above.

We believe this provision benefits us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees or agents. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition or results of operations.

General Risks

A pandemic, epidemic or outbreak of an infectious disease in the United States may adversely affect our business.

If a pandemic, epidemic or outbreak of an infectious disease occurs in the United States or worldwide, our business may be adversely affected. In March 2020, SARS-CoV-2 (severe acute respiratory syndrome 2), or coronavirus, a novel strain of virus which causes coronavirus disease, or COVID-19, was declared a pandemic by the World Health Organization. The continued worldwide spread of COVID-19 has impacted the global economy and may impact our operations, including the potential interruption of our clinical trial activities, regulatory reviews and our supply chain. We are monitoring the global outbreak and spread of the novel strain of COVID-19 and have taken steps to identify and mitigate the adverse impacts on, and risks to, our business posed by its spread and actions taken by governmental and health authorities to address this pandemic. To date, our financial condition and operations have not been significantly impacted by the COVID-19 pandemic; however the spread of COVID-19 has caused us to modify our business practices, including implementing a work from home policy for all employees who are able to perform their duties remotely and restricting all nonessential travel, and we expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees and other business partners in light of COVID-19.

In addition, the COVID-19 outbreak has delayed our ongoing Phase 1b clinical trial evaluating the safety and tolerability of KarXT in healthy elderly volunteers. Topline results from this trial were expected by the end of 2020, but as a result of COVID-19's impact on enrollment, we now anticipate that topline results from this trial will be announced in the second quarter of 2021. While COVID-19 has not affected the anticipated timing of our other planned clinical trials, including the initiation of the Phase 3 EMERGENT program in 2020, we continue to monitor the impact of COVID-19 across all clinical trials, particularly in the elderly population.

Furthermore, the spread of the virus may affect the operations of key governmental agencies, such as the FDA, which may delay the development of our product candidates. The spread of an infectious disease, including COVID-19, may also result in the inability of our suppliers to deliver components or raw materials on a timely basis or at all. In addition, hospitals may reduce staffing and reduce or postpone certain treatments in response to the spread of an infectious disease. Such events may result in a period of business disruption, and in reduced operations, or doctors and medical providers may be unwilling to participate in our clinical trials, any of which could materially affect our business, financial condition and results of operations.

The extent to which the coronavirus impacts our business beyond those impacts already sustained will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of the coronavirus and the actions to contain the coronavirus or treat its impact, among others. The coronavirus and other infectious diseases could result in a widespread health crisis that could adversely affect the economies and financial markets worldwide, resulting in an economic downturn that could impact our business, financial condition, and results of operations.

Two vaccines for COVID-19 were granted Emergency Use Authorization by the FDA in late 2020, and more are likely to be authorized in the coming months. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials, which could lead to delays in these trials.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved, or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the 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 biologics or modifications to approved biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

In response to the COVID-19 pandemic, on March 10, 2020 the FDA announced its intention to postpone most inspections of foreign manufacturing facilities while local, national and international conditions warrant. On March 18, 2020, the FDA announced its intention to temporarily postpone routine surveillance inspections of domestic manufacturing facilities and provided guidance regarding the conduct of clinical trials which the FDA continues to update. Additionally, as of June 23, 2020, the FDA noted it is continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals; however, FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions FDA is unable to complete such required inspections during the review period. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If the FDA becomes unable to continue its current level of performance, we could experience delays and setbacks for our product candidates and for any approvals we may seek which could adversely affect our business.

Cyber-attacks or other failures in our telecommunications or information technology systems, or those of our collaborators, contract research organizations, third-party logistics providers, distributors or other contractors or consultants, could result in information theft, data corruption and significant disruption of our business operations.

We, our collaborators, our CROs, third-party logistics providers, distributors and other contractors and consultants utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including third parties gaining access to employee accounts using stolen or inferred credentials, computer malware, viruses, spamming, phishing attacks or other means, and deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our, our collaborators', our CROs', third-party logistics providers', distributors' and other contractors' and consultants' systems and networks, and the confidentiality, availability and integrity of our data. There can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack, data

breach or destruction or loss of data could result in a violation of applicable U.S. and international privacy, data protection and other laws, and subject us to litigation and governmental investigations and proceedings by federal, state and local regulatory entities in the United States and by international regulatory entities, resulting in exposure to material civil and/or criminal liability. Further, our general liability insurance and corporate risk program may not cover all potential claims to which we are exposed and may not be adequate to indemnify us for all liability that may be imposed, and could have a material adverse effect on our business and prospects. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials for any of our product candidates could result in delays in our development and regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to implement further data protection measures.

Sales of a substantial number of our common stock in the public market could cause our share price to fall.

Sales of a substantial number of our common stock in the public market or the perception that these sales might occur could depress the market price of our common shares, could make it more difficult for you to sell your common stock at a time and price that you deem appropriate and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

ITEM 2. PROPERTIES

Our headquarters are located at 33 Arch Street, Suite 3110, Boston, Massachusetts, where we occupied approximately 11,225 square feet of leased office space as of December 31, 2020. This lease expires in December 2023.

Additionally, in February 2020, we opened an office located at 11711 N. Meridian Street, Suite 430, Carmel, Indiana, consisting of 5,050 square feet of leased office space. This lease expires in July 2023.

ITEM 3. LEGAL PROCEEDINGS

We are not currently subject to any material legal proceedings.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol "KRTX" on the Nasdaq Global Select Market and has been publicly traded since June 28, 2019. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of February 15, 2021, there were approximately 7 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

Securities Authorized for Issuance Under Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Recent Sales of Unregistered Securities

We deemed the grants and exercises of stock options issued under our equity compensation plans prior to the completion of our initial public offering in July 2019 to be exempt from registration in reliance on Rule 701 of the Securities Act as offers and sales of securities under compensatory benefit plans and contracts relating to compensation. Each of the recipients of securities in any transaction exempt from registration either received or had adequate access, through employment, business or other relationships, to information about us.

Issuer Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. RESERVED

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes included at the end of this Annual Report on Form 10-K. This discussion and other parts of this Annual Report on Form 10-K contain forward-looking statements that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company driven to create and deliver transformative medicines for people living with psychiatric and neurological conditions. Our pipeline is built on the broad therapeutic potential of our lead product candidate, KarXT, an oral modulator of muscarinic receptors that are located both in the central nervous system, or CNS, and various peripheral tissues. KarXT is our proprietary product candidate that combines xanomeline, a novel muscarinic agonist, with trospium, an approved muscarinic antagonist, to preferentially stimulate muscarinic receptors in the CNS.

Since our inception in 2009, we have focused substantially all of our efforts and financial resources on organizing and staffing our company, acquiring and developing our technology, raising capital, building our intellectual property portfolio, undertaking preclinical studies and clinical trials and providing general and administrative support for these activities.

On July 2, 2019, we issued and sold 6,414,842 shares of our common stock, including full exercise of the underwriters' over-allotment option to purchase an additional 836,718 shares, at a public offering price of $16.00 per share, in our initial public offering, or IPO. The aggregate net proceeds to us from the IPO were $93.0 million.

On November 25, 2019, we issued and sold 2,600,000 shares of our common stock at a public offering price of $96.00 per share in a follow-on offering in which we received net proceeds of approximately $234.2 million. Prior to the IPO and follow-on public offering, we funded our operations primarily with proceeds from the sales of redeemable convertible preferred stock and the issuance of convertible notes.

On July 2, 2020, we filed an automatically effective registration statement on Form S-3, or the Registration Statement, with the SEC which registers the offering, issuance and sale of an unspecified amount of common stock, preferred stock, debt securities, warrants and/or units of any combination thereof. We simultaneously entered into an equity distribution agreement with Goldman Sachs & Co. LLC, as sales agent, to provide for the issuance and sale by the Company of up to $150.0 million of common stock from time to time in "at-the-market" offerings under the Registration Statement and related prospectus filed with the Registration Statement, or the ATM Program. As of December 31, 2020, no sales had been made pursuant to the ATM Program.

We have never generated revenue and have incurred significant net losses since inception. Our net losses were $68.6 million, $44.0 million and $17.5 million for the years ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $144.1 million. Our net losses may fluctuate significantly from quarter to quarter and year to year. We expect to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our operating expenses and capital expenditures will increase substantially, particularly as we:

- invest significantly to further develop KarXT for our current and future indications;
- advance additional product candidates into preclinical and clinical development;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;

- require the manufacture of larger quantities of our product candidates for clinical development and potential commercialization;
- hire additional clinical, scientific, management and administrative personnel;
- maintain, expand and protect our intellectual property portfolio;
- acquire or in-license other assets and technologies; and
- add additional operational, financial and management information systems and processes to support our ongoing development efforts, any future manufacturing or commercialization efforts and our ongoing operations as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for a product candidate, which we expect will take a number of years, if ever, and the outcome of which is subject to significant uncertainty. Additionally, we currently use third parties such as contract research organizations, or CROs, and contract manufacturing organizations, or CMOs, to carry out our preclinical and clinical development activities, and we do not yet have a sales organization. If we obtain regulatory approval for any product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of private and public equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements with third parties. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates.

As of December 31, 2020, we had cash, cash equivalents and available-for-sale investments of $322.3 million. We believe that our existing cash, cash equivalents and available-for-sale investments will be sufficient to meet our anticipated operating and capital expenditure requirements into 2023. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See “—Liquidity and Capital Resources.”

Components of Our Results of Operations

Revenue

To date, we have not generated any revenue and do not expect to generate any revenue in the foreseeable future, if at all. If our development efforts for our product candidates are successful and result in regulatory approval, we may generate revenue in the future from product sales. If we enter into license or collaboration agreements for any of our product candidates or intellectual property, we may generate revenue in the future from payments as a result of such license or collaboration agreements. We cannot predict if, when, or to what extent we will generate revenue from the commercialization and sale of our product candidates. We may never succeed in obtaining regulatory approval for any of our product candidates.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of our product candidates and our drug discovery efforts, which include:

- personnel costs, including salaries and the related costs, and stock-based compensation expense, for employees engaged in research and development functions;
- expenses incurred in connection with the preclinical and clinical development of our product candidates, including under agreements with CROs;

- expenses incurred in connection with CMOs that manufacture drug products for use in our preclinical and clinical trials;
- formulation costs and chemistry, manufacturing and controls, or CMC, costs; and
- expenses incurred under agreements with consultants who supplement our internal capabilities.

We expense all research and development costs in the periods in which they are incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and third-party service providers.

We do not track certain research and development expenses on an indication-by-indication basis as they primarily relate to personnel or other consulting and service costs, which are deployed across multiple projects under development. These costs are included in unallocated research and development expenses in the table below. Other research and development costs, such as fees paid to consultants, central laboratories, contractors, CMOs and CROs in connection with our clinical development activities, are tracked on an indication-by-indication basis. Formulation and CMC costs as well as preclinical expenses consist of costs associated with activities to support our current and future clinical programs, but are not allocated on an indication-by-indication basis due to the overlap of the potential benefit of those efforts across multiple indications that utilize KarXT and future product and development candidates. The following table summarizes our research and development expenses:

	Year Ended December 31,		
	2020	2019	2018
Schizophrenia clinical trials	$ 11,803	$ 13,455	$ 8,160
Pain clinical trials	1,297	619	—
DRP clinical trials	1,465	381	—
Formulation and CMC	8,987	1,871	1,130
Preclinical	898	1,908	540
Discovery	5,555	1,123	—
Unallocated expenses	13,403	5,179	1,706
Total research and development expense	$ 43,408	$ 24,536	$ 11,536

We expect our research and development expenses to increase substantially for the foreseeable future as we continue to invest in research and development activities related to developing our product candidates, including investments in manufacturing, as our programs advance into later stages of development and we continue to conduct clinical trials. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming, and the successful development of our product candidates is highly uncertain.

Because of the numerous risks and uncertainties associated with conducting product development, we cannot determine with certainty the duration and completion costs of our current or future preclinical studies and clinical trials or if, when, or to what extent we will generate revenues from the commercialization and sale of our product candidates. We may never succeed in achieving regulatory approval for our product candidates. The duration, costs and timing of preclinical studies and clinical trials and development of our product candidates will depend on a variety of factors, if and as we:

- continue to develop and conduct clinical trials for KarXT for our current and future indications;
- initiate and continue research, preclinical and clinical development efforts for future product candidates;
- seek to identify additional product candidates;
- seek regulatory approvals for KarXT for our current and future indications as well as any other product candidates that successfully complete clinical development;

- add operational, financial and management information systems and personnel, including personnel to support our product development;
- hire and retain additional personnel, such as clinical, quality control, scientific, commercial and administrative personnel;
- maintain, expand and protect our intellectual property portfolio;
- establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval, if any;
- assess the potential impact of the COVID-19 pandemic on the ability to execute research and development activities;
- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other product candidates and technologies.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any of our product candidates.

We do not believe that it is possible at this time to accurately project total indication-specific expenses through commercialization. There are numerous factors associated with the successful commercialization of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development. Additionally, future commercial and regulatory factors beyond our control will impact our clinical development programs and plans.

General and Administrative Expenses

General and administrative expenses consist primarily of employee-related costs for personnel in executive, finance, commercial, and administrative functions, costs related to maintenance and filing of intellectual property, facility-related costs, insurance costs, and other expenses for outside professional services, including legal, human resources, data management, audit and accounting services, and costs incurred as we prepare for commercialization. Personnel costs consist of salaries, benefits, travel expense and stock-based compensation expense.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates, and as we commercialize. We will also incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs as well as investor and public relations expenses associated with operating as a public company.

Other Income (Expense), Net

Interest Income. Interest income consists of interest income from our cash equivalents and available-for-sale investments.

Interest Income (Expense), Net. Interest income (expense), net, consists of interest accrued, net of any interest forgiven, on the principal balance of convertible notes that were issued and outstanding during 2019 and 2018. In August 2018, March 2019 and April 2019, all outstanding convertible notes were converted into redeemable convertible preferred stock. A portion of the accrued interest was forgiven with respect to certain of the convertible notes upon their conversion into redeemable convertible preferred stock, and the forgiven interest was recorded as a reduction to interest expense in the years ended December 31, 2019 and 2018.

Accretion of Debt Discount. Upon issuance of our convertible notes, each note was recorded at cost, net of the derivative liability. This discount on each outstanding note, if any, was amortized as interest expense to the date such note was expected to convert using the effective interest rate method and is reflected in the statements of operations as accretion of debt discount.

Change in Fair Value of Derivative. Our convertible notes contained conversion options at a significant premium that were deemed to be embedded derivatives which are required to be bifurcated and accounted for separately from the convertible note. We remeasured the derivative liability to fair value at each reporting date, and we recognized changes in the fair value of the derivative liabilities in our statements of operations. As part of the conversion of outstanding convertible notes into redeemable convertible preferred stock, all derivatives were settled in March and April 2019.

Results of Operations

Comparison of the Years Ended December 31, 2020 and 2019

	Year Ended December 31,		
	2020	2019	Change
		(in thousands)	
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	43,408	24,536	18,872
General and administrative	28,408	20,869	7,539
Total operating expenses	71,816	45,405	26,411
Loss from operations	(71,816)	(45,405)	(26,411)
Total other income, net	3,305	1,448	1,857
Income tax provision	(43)	—	(43)
Net loss attributable to common stockholders	$ (68,554)	$ (43,957)	$ (24,597)

Research and Development Expenses

	Year Ended December 31,		
	2020	2019	Change
		(in thousands)	
Direct research and development expenses:			
Schizophrenia clinical trials	$ 11,803	$ 13,455	$ (1,652)
Pain clinical trials	1,297	619	678
Dementia-related psychosis clinical trials	1,465	381	1,084
Formulation and CMC	8,987	1,871	7,116
Preclinical	898	1,908	(1,010)
Discovery	5,555	1,123	4,432
Unallocated expenses:			
Personnel related (including stock-based compensation)	11,134	3,495	7,639
Consultant fees and other expenses	2,269	1,684	585
Total research and development expense	$ 43,408	$ 24,536	$ 18,872

Expenses related to our schizophrenia clinical trials decreased by $1.7 million due to the conclusion of EMERGENT-1, which was partially offset by expenses related to startup activities for our planned EMERGENT Phase 3 clinical trials, including the initiation of EMERGENT-2 in December 2020. The decrease was further offset by a one-time $2 million milestone payment made to PureTech Health which was expensed in December 2020, upon initiation of our EMERGENT-2 trial in accordance with the PureTech License Agreement (see Note 11 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K). The increase of $0.7 million and $1.1 million in expenses related to pain and DRP clinical trials, respectively, consist of enrollment and dosing activities for our Phase 1b trials incurred in 2020. Formulation and CMC expenses increased by $7.1 million due to an increase in manufacturing activities to obtain sufficient supply to support clinical trial activities, including our planned EMERGENT Phase 3 clinical trials. Preclinical expenses decreased by $1.0 million due to the conclusion of several toxicology studies in 2019. The increase of $4.4

million in expenses related to our discovery program was due to an increase in ongoing discovery efforts, including our ongoing collaborations with Charles River Labs and Psychogenics, Inc. The increase of $7.6 million in personnel-related costs was primarily a result of an increase in headcount. The increase of $0.6 million in consultant fees and other expenses consists of an increase in other consulting costs not specifically allocated to clinical, preclinical, formulation and CMC activities.

General and Administrative Expenses

	Year Ended December 31,		
	2020	2019	Change
		(in thousands)	
Personnel-related (including stock-based compensation)	$ 16,701	$ 15,750	$ 951
Professional and consultant fees	5,162	2,130	3,032
Other	6,545	2,989	3,556
Total general and administrative expense	$ 28,408	$ 20,869	$ 7,539

The increase of $1.0 million in personnel-related costs was primarily a result of an increase in headcount, partially offset by the unrepeated acceleration of stock option awards which fully vested prior to the end of 2019 as a result of our Series B preferred stock financing and IPO. The increase of $3.0 million in professional and consultant fees was primarily due to an increase in recruiting fees, accounting fees, legal costs, and consulting fees related to our ongoing business activities. The increase of $3.6 million in other costs was primarily due to insurance costs, the expansion of our facility in Boston, Massachusetts, and the entry into a new office lease in Carmel, Indiana.

Other Income, Net

	Year Ended December 31,		
	2020	2019	Change
		(in thousands)	
Interest income	$ 3,305	$ 2,517	$ 788
Interest income, net	—	11	(11)
Accretion of debt discount	—	(945)	945
Change in fair value of derivative	—	(135)	135
Total other income, net	$ 3,305	$ 1,448	$ 1,857

The increase in interest income is attributable to interest earned on our cash equivalents and available-for-sale investments, the balance of which increased significantly subsequent to our IPO in July 2019 and our follow-on offering in November 2019. This increase in interest income was partially offset by lower interest rates throughout 2020.

There was no interest income, net, accretion of debt discount, or change in fair value of derivative recorded during 2020 because there were no convertible notes outstanding during the period.

Interest income, net, for the year ended December 31, 2019 represents the excess of interest forgiven over interest accrued on the 2018 Convertible Note when all outstanding principal under the 2018 Convertible Note was converted into shares of Series B convertible preferred stock in March and April 2019.

Accretion of debt discount for the year ended December 31, 2019 represents the full accretion of debt discount when all outstanding principal under the 2018 Convertible Note was converted into shares of Series B convertible preferred stock in March and April 2019.

The change in fair value of derivative for the year ended December 31, 2019 reflects the mark-to-market of the convertible note derivative liabilities prior to the conversion of the outstanding principal under the 2018 Convertible Note in March and April 2019 into shares of our Series B convertible preferred stock.

Comparison of the Years Ended December 31, 2019 and 2018

	Year Ended December 31,		
	2019	2018	Change
		(in thousands)	
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	24,536	11,536	13,000
General and administrative	20,869	2,974	17,895
Total operating expenses	45,405	14,510	30,895
Loss from operations	(45,405)	(14,510)	(30,895)
Total other income (expense), net	1,448	(3,002)	4,450
Net loss attributable to common stockholders	$ (43,957)	$ (17,512)	$ (26,445)

Research and Development Expenses

	Year Ended December 31,		
	2019	2018	Change
		(in thousands)	
Direct research and development expenses:			
Schizophrenia clinical trials	$ 13,455	$ 8,160	$ 5,295
Pain clinical trials	619	—	619
Dementia-related psychosis clinical trials	381	—	381
Formulation and CMC	1,871	1,130	741
Preclinical	1,908	540	1,368
Discovery	1,123	—	1,123
Unallocated expenses:			
Personnel related (including stock-based compensation)	3,495	947	2,548
Consultant fees and other expenses	1,684	759	925
Total research and development expense	$ 24,536	$ 11,536	$ 13,000

Expenses related to our schizophrenia clinical trials increased by $5.3 million due to the progress of EMERGENT-1, for which topline data was announced in November 2019. The increase of $0.6 million and $0.4 million in expenses related to pain and DRP clinical trials, respectively, consist of study preparation and startup costs for Phase 1b clinical trials incurred in the year ended December 31, 2019. Formulation and CMC expenses increased by $0.7 million due to an increase in formulation development activities. Preclinical expenses increased by $1.4 million due to the initiation and execution of toxicology studies. The increase of $1.1 million related to our discovery program was due to the startup of various discovery efforts and related consulting costs. The increase of $2.5 million in personnel-related costs was primarily a result of an increase in headcount. The increase of $0.9 million in consultant fees and other expenses was due to an increase in other consulting costs not specifically allocated to preclinical, clinical, formulation and CMC activities.

General and Administrative Expenses

	Year Ended December 31,		
	2019	2018	Change
		(in thousands)	
Personnel-related (including stock-based compensation)	$ 15,750	$ 1,564	$ 14,186
Professional and consultant fees	2,130	999	1,131
Other	2,989	411	2,578
Total general and administrative expense	$ 20,869	$ 2,974	$ 17,895

The increase of $14.2 million in personnel-related costs was primarily due to an increase in stock-based compensation of $11.2 million, which was primarily due to the acceleration of stock option awards which fully vested prior to the end of 2019 as a result of our Series B preferred stock financing and our IPO. The increase of $1.1 million in professional and consultant fees was primarily due to an increase in audit fees, legal costs, public relations consulting fees, and recruiting costs related to our preparations to be, and our ongoing business activities as, a public company. The increase of $2.6 million in other costs was primarily due to insurance costs and our facility lease in Boston, Massachusetts.

Other Income (Expense), Net

	Year Ended December 31,		
	2019	2018	Change
		(in thousands)	
Interest income	$ 2,517	$ 25	$ 2,492
Interest income (expense), net	11	(407)	418
Accretion of debt discount	(945)	(2,176)	1,231
Change in fair value of derivative	(135)	(444)	309
Total other income (expense), net	$ 1,448	$ (3,002)	$ 4,450

Interest income is attributable to interest earned on our cash equivalents and short-term investments, which were purchased beginning in November 2018.

Interest income (expense), net, for the year ended December 31, 2019 represents the excess of interest forgiven over interest accrued on the 2018 Convertible Note when all outstanding principal under the 2018 Convertible Note was converted into shares of Series B convertible preferred stock in March and April 2019. Interest income (expense), net, for the year ended December 31, 2018 represents the excess of interest accrued on the 2018 Convertible Note and the Convertible Notes over interest forgiven on such notes when all outstanding principal under such notes was converted into shares of Series A convertible preferred stock in August 2018.

Accretion of debt discount for the year ended December 31, 2019 represents the full accretion of debt discount when all outstanding principal under the 2018 Convertible Note was converted into shares of Series B convertible preferred stock in March and April 2019. The accretion of debt discount for the year ended December 31, 2018 represents the full accretion of debt discount when all outstanding principal under the 2018 Convertible Note and the Convertible Notes was converted into shares of Series A convertible preferred stock in August 2018, as well as the accretion of debt discount for debt issuances under the 2018 Convertible Note that were issued after such conversion.

The change in fair value of derivative for the year ended December 31, 2019 reflects the mark-to-market of the convertible note derivative liabilities prior to the conversion of the outstanding principal under the 2018 Convertible Note in March and April 2019 into shares of our Series B convertible preferred stock. The change in fair value of derivative for the year ended December 31, 2018 reflects the mark-to-market of the convertible note derivative liabilities prior to the conversion of the outstanding principal under the 2018 Convertible Note

and the Convertible Notes in August 2018 into shares of our Series A convertible preferred stock, as well as the mark-to-market of the convertible note derivative liabilities recognized for debt issuances under the 2018 Convertible Note which were issued after such conversion.

Income Taxes

We have not recorded any income tax benefits for the net losses we incurred or for the research and development tax credits we generated during the years ended December 31, 2020, 2019 and 2018 as we believed, based upon the weight of available evidence, that it was more likely than not that all of the net operating loss carryforwards and tax credits will not be realized. At December 31, 2020, we had federal net operating loss carryforwards totaling $179.8 million, of which $9.7 million begin to expire in 2029 and $170.1 million can be carried forward indefinitely. At December 31, 2020, we had state net operating loss carryforwards totaling $151.7 million which begin to expire in 2030. The federal and state operating loss carryforwards may be available to offset future income tax liabilities. As of December 31, 2020, we also had federal and state research and development tax credit carryforwards of $5.0 million and $0.8 million, respectively, which begin to expire in 2031. Through December 31, 2020, we had recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

We filed federal and state taxes as part of a controlled group with PureTech Health LLC, or PureTech Health, a related party, until the closing of our Series A financing in August 2018. Following the financing, we no longer met the requirements to be included in the controlled group filing, as PureTech Health no longer held 80% of our outstanding voting securities. Therefore, from that date onward, we were required to file a separate U.S. federal income tax return. On July 2, 2019, PureTech no longer held 50% of the outstanding shares of the Company. As such, we have filed separate state income tax returns subsequent to this date.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We have not yet commercialized any of our product candidates and we do not expect to generate revenue from sales of any product candidates for several years, if at all. To date, we have funded our operations primarily with proceeds from the sale of redeemable convertible preferred stock, issuance of convertible notes, and sales of our common stock. Through December 31, 2020, our operations have been financed by gross proceeds of $25.7 million from the issuance of convertible notes, $91.0 million from the sale of shares of our redeemable convertible preferred stock, $93.0 million from the sale of our common stock in our initial public offering, and $234.2 million from the sale of our common stock in a follow-on public offering. As of December 31, 2020, we had $322.3 million in cash, cash equivalents and available-for-sale investments, and an accumulated deficit of $144.1 million.

On July 2, 2020, we filed the Registration Statement with the SEC and simultaneously entered into an equity distribution agreement with Goldman Sachs & Co. LLC, as sales agent, for the ATM Program. As of December 31, 2020, no sales had been made pursuant to the ATM Program.

Our primary use of cash has been to fund operating expenses, which consist of research and development and general and administrative expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	Year Ended December 31,		
	2020	2019	2018
	(in thousands)		
Net cash used in operating activities	$ (69,856)	$ (30,923)	$ (15,377)
Net cash used in investing activities	(89,650)	(174,335)	(5,115)
Net cash provided by financing activities	3,659	405,283	27,577
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (155,847)	$ 200,025	$ 7,085

Cash Flows from Operating Activities

Cash used in operating activities for the year ended December 31, 2020 was $69.9 million, consisting of a net loss of $68.6 million adjusted for noncash items, including stock-based compensation of $13.5 million, interest expense resulting from the net amortization of premiums and discounts on investment securities of $0.6 million, and changes in our net operating assets and liabilities, including an increase in accrued expenses of $2.8 million and an increase in prepaid and other current assets of $18.6 million, which was primarily due to timing of payments related to startup activities for our planned EMERGENT Phase 3 clinical trials, including the initiation of EMERGENT-2 in December 2020, as well as timing of payment of other research and development and general and administrative expenses.

Cash used in operating activities for the year ended December 31, 2019 was $30.9 million, consisting of a net loss of $44.0 million adjusted for noncash items, including stock-based compensation expense of $12.6 million, interest income resulting from the net accretion of premiums and discounts on investment securities of $0.8 million, the accretion of debt discount related to the convertible notes of $0.9 million, and changes in our net operating assets and liabilities, including an increase in accrued expenses of $1.8 million as well as an increase in prepaid expenses and other current assets of $1.6 million, due primarily to timing of payment of various research and development and general and administrative expenses.

Cash used in operating activities for the year ended December 31, 2018 was $15.4 million, consisting of a net loss of $17.5 million partially adjusted for noncash items, including stock-based compensation expense of $1.0 million, the accretion of debt discount related to the convertible notes of $2.2 million, and changes in our net operating assets and liabilities, including an increase in prepaid expenses and other current assets of $1.5 million due primarily to timing of payment of research and development and general and administrative expenses.

Cash Flows from Investing Activities

Cash used in investing activities for the year ended December 31, 2020 was $89.7 million, consisting primarily of $344.2 million for the purchases of investment securities, partially offset by maturities of investment securities of $255.0 million.

Cash used in investing activities for the year ended December 31, 2019 was $174.3 million, consisting primarily of $231.7 million for the purchases of investment securities, partially offset by maturities of investment securities of $50.0 million and sales of investment securities of $7.5 million.

Cash used in investing activities for the year ended December 31, 2018 was approximately $5.1 million and consisted primarily of $5.0 million for the purchases of investment securities.

Cash Flows from Financing Activities

Cash provided by financing activities for the year ended December 31, 2020 was $3.7 million and was attributable to proceeds from the exercise of stock options of $4.1 million, offset by $0.4 million in payments of deferred offering costs associated with the filing of our Shelf and the ATM Program prospectus.

Cash provided by financing activities for the year ended December 31, 2019 was $405.3 million and was related primarily to $234.6 million of proceeds from the sale of our common stock in our follow-on public offering (net of $15.0 million in underwriting discounts and commissions) partially offset by $0.4 million in payments of follow-on offering costs, $95.5 million of proceeds from the sale of our common stock in our initial public offering (net of $7.2 million in underwriting discounts and commissions) partially offset by $2.4 million in payments of initial public offering costs, $74.8 million of net proceeds from the issuance of redeemable convertible preferred stock, as well as $3.1 million related to proceeds from the issuance of convertible notes.

Cash provided by financing activities for the year ended December 31, 2018 was $27.6 million and was related to the $15.9 million of net proceeds from the issuance of redeemable convertible preferred stock and $11.7 million of proceeds from the issuance of convertible notes.

Future Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, in particular as we continue to advance our product candidates through clinical trials. In addition, we expect to incur additional costs associated with our ongoing operations as a public company.

As of December 31, 2020, we had cash, cash equivalents and available-for-sale investments of $322.3 million. Based on our current plans, we believe that our existing cash, cash equivalents and available-for-sale investments will be sufficient to meet our anticipated operating and capital expenditure requirements into 2023.

We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical product candidates, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements will depend on and could increase significantly as a result of many factors, including:

- the scope, progress, results and costs of researching and developing KarXT for our current and future indications as well as other product candidates we may develop;
- the timing of, and the costs involved in, obtaining marketing approvals for KarXT for our current and future indications as well as future product candidates we may develop and pursue;
- the number of future indications and product candidates that we pursue and their development requirements;
- if approved, the costs of commercialization activities for KarXT for the approved indication, or any other product candidate that receives regulatory approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of regulatory approval, revenue, if any, received from commercial sales of KarXT for any program or revenues received from any future product candidates;
- the extent to which we in-license or acquire rights to other products, product candidates or technologies;
- our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure;

- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights including enforcing and defending intellectual property related claims; and
- the costs of operating as a public company.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. Further, our operating plans may change in the future, and we may need additional funds to meet operational needs and capital requirements associated with such operating plans.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity financings, debt financings, collaborations with other companies or other strategic transactions. We do not currently have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect their rights as 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 acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing 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. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Further, our operating plans may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials and other research and development activities. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated product development programs.

Contractual Obligations and Other Commitments

The following table summarizes our outstanding contractual obligations as of payment due date by period at December 31, 2020.

	Payments Due by Period				
	Total	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
	(in thousands)				
Operating lease commitments(1)	$ 2,932	$ 982	$ 1,950	$ —	$ —
Total	$ 2,932	$ 982	$ 1,950	$ —	$ —

(1) Reflects payments due for our lease of office space in Boston, Massachusetts, under an operating lease agreement that expires in December 2023, as amended, and payments due for our lease of office space in Carmel, Indiana, under an operating lease agreement that expires in July 2023.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. These contracts are cancelable by us upon prior written notice. Payments due upon cancellation consist of various termination penalties, and payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

We are also party to certain license and collaboration agreements with PureTech Health and Eli Lilly and Company. We have not included certain future payments which are contingent upon future events such as our achievement of specified regulatory and commercial milestones, or royalties on net product sales under these agreements in the table of contractual obligations above since as of December 31, 2020, we were unable to estimate the timing or likelihood of achieving these milestones or generating future product sales.

Critical Accounting Polices and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value 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 that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Research and Development Contract Costs and Accruals

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. We accrue for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of preclinical studies and clinical trials, and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated amount of services provided and include these costs in accrued liabilities in the balance sheets and within research and development expense in the statements of operations. When evaluating the adequacy of the accrued liabilities, we analyze progress of the research studies or clinical trials and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from our estimates. Our historical accrual estimates have not been materially different from the actual costs.

Convertible Notes and Derivative Liabilities

In June 2018, the Company entered into an agreement with Wellcome Trust to receive up to $8.0 million in gross proceeds from the issuance of a convertible note. The Company received $2.0 million of proceeds in July 2018, $2.7 million in November 2018, $1.6 million in March 2019, and $1.6 million in April 2019.

In addition, since inception and through December 31, 2018, the Company has issued $14.0 million of convertible notes to other parties, of which $13.5 million were issued to PureTech Health, a related party (see Note 13 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K). During the year ended December 31, 2018, the Company issued Convertible Notes to PureTech Health with principal totaling $7.0 million.

All outstanding convertible notes were converted into Series A convertible preferred stock and Series B convertible preferred stock in August 2018, March 2019 and April 2019. As of December 31, 2020, there were no convertible notes outstanding. See Note 5 to the consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for additional detail.

The convertible notes issued contained conversion options at a significant discount that we determined to be embedded derivatives, which were recorded as liabilities on our balance sheet and remeasured to fair value at each reporting date until each derivative was settled. Changes in the fair value of the derivative liabilities were recognized as change in fair value of derivative in the statement of operations. The fair value of the derivative liabilities was determined at each period by assessing the likelihood and timing of events that would result in either a conversion or change-of-control feature being triggered, as well as changes in market conditions.

Because there were no convertible notes issued or outstanding during the year ended December 31, 2020, this is no longer considered to be a critical accounting policy as of and for the year ended December 31, 2020.

Stock-Based Compensation Expense

Prior to our IPO, the estimated fair value of our common stock had been determined by our board of directors as of the date of each award grant, with input from management, considering our most recently available third-party valuations of common stock and our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. Subsequent to our IPO, the fair value of our common stock is based on quoted market prices. The determination of the fair value of share-based payment awards utilizing the Black-Scholes model is affected by our stock price and a number of assumptions, including expected volatility, expected life, risk-free interest rate and expected dividends.

Expected Term—We have opted to use the "simplified method" for estimating the expected term of employee options, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option (generally 10 years).

Expected Volatility—Due to our limited operating history and a lack of 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. The historical volatility data was computed using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards.

Risk-Free Interest Rate—The risk-free rate assumption is based on the U.S. Treasury instruments with maturities similar to the expected term of our stock options.

Expected Dividend—We have not issued any dividends and do not expect to issue dividends over the life of the options. As a result, we have estimated the dividend yield to be zero.

The estimated fair value of stock options granted to employees and non-employee service providers are expensed over the requisite service period (generally the vesting term) on a straight-line basis. We account for the impact of forfeitures as they occur.

The assumptions underlying these valuations represent management's best estimates, which involve inherent uncertainties and the application of management judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our share-based compensation expense could be materially different.

Because the fair value of our common stock is based on quoted market prices subsequent to our IPO, stock-based compensation expense is not considered to be a critical accounting policy as of and for the year ended December 31, 2020.

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 in the rules and regulations of the Securities and Exchange Commission.

JOBS Act Accounting Election

As of June 30, 2020, the market value of our common stock held by non-affiliates exceeded $700 million, and as a result, as of January 1, 2021, we no longer qualified as an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As a large accelerated filer, we are subject to certain disclosure requirements that are applicable to other public companies that were not applicable to us as an emerging growth company, including compliance with the auditor attestation requirements in the assessment of our internal control over financial reporting imposed by the Sarbanes-Oxley Act of 2002, compliance 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 and full disclosure obligations regarding executive compensation. Additionally, we are no longer able to take advantage of transition periods for complying with new or revised accounting standards that are available to emerging growth companies.

Recently Issued and Adopted Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and available-for-sale investment securities of $322.3 million as of December 31, 2020, which consisted primarily of money market funds and investment securities, largely composed of U.S. Treasuries and investment grade, short to intermediate term fixed income securities.

The primary objective of our investment activities is to preserve capital to fund our operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of investments in a variety of securities of high credit quality and short-term duration, according to our board-approved investment policy. Our investments are subject to interest rate risk and could fall in value if market interest rates increase. A hypothetical 10% relative change in interest rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with vendors that are located outside of the United States. As a result, our operations may be subject to fluctuations in foreign currency exchange rates in the future.

Inflation generally affects us by increasing our cost of labor. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2020, 2019 and 2018.

ITEM 8. CONSOLIDATED FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm	119
Consolidated Balance Sheets as of December 31, 2020 and 2019	122
Consolidated Statements of Operations for the years ended December 31, 2020, 2019 and 2018	123
Consolidated Statements of Comprehensive Loss for the years ended December 31, 2020, 2019 and 2018	124
Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit) for the years ended December 31, 2020, 2019 and 2018	125
Consolidated Statements of Cash Flows for the years ended December 31, 2020, 2019 and 2018	126
Notes to Consolidated Financial Statements	127

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and Board of Directors
Karuna Therapeutics, Inc.:

Opinions on the Consolidated Financial Statements and Internal Control Over Financial Reporting

We have audited the accompanying consolidated balance sheets of Karuna Therapeutics, Inc. and subsidiary (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the years in the three-year period ended December 31, 2020, and the related notes (collectively, the consolidated financial statements). We also have audited the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020 based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's consolidated financial statements and an opinion on the Company's internal control over financial reporting 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 audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements 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. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control Over Financial Reporting

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

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

Critical Audit Matter

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

Evaluation of prepaid research and development contract costs

As discussed in Note 2 to the consolidated financial statements, the Company incurs costs for research and development activities conducted by third-party service providers, which include the conduct of preclinical studies and clinical trials, and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated amount of services provided by analyzing progress of the research studies or clinical trials and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred. Advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. As of December 31, 2020, prepaid research and development expenses totaled $18.7 million as discussed in Note 4 to the consolidated financial statements.

We identified the evaluation of prepaid research and development contract costs as a critical audit matter. Specifically, the amount was based on certain assumptions and inputs, including the status of research and development activities and the associated percentage of completion, estimated costs per patient, the number and status of patients enrolled, as well as invoices received and paid. Subjective auditor judgment was required to evaluate these assumptions and inputs.

The following are the primary procedures we performed to address this critical audit matter. We evaluated the design and tested the operating effectiveness of certain internal controls related to the research and development contract process. This included a control related to the assumptions and inputs described above. We selected certain research and development contracts and assessed the Company's estimate of the cost of activities completed to date by:

- inquiring of management, including the internal project managers responsible for monitoring and tracking the status of clinical trials
- examining underlying documentation and third-party evidence from clinical research organizations, and comparing them to management's assumptions and inputs
- obtaining and inspecting executed change orders and original contract terms, including the timeline and budget, and agreeing them to the information used in the Company's estimation of research and development costs incurred to date
- examining certain invoices received after December 31, 2020 and evaluating whether services received prior to December 31, 2020 were included in the Company's estimate of costs incurred as of December 31, 2020.

/s/ KPMG LLP

We have served as the Company's auditor since 2018.

Boston, Massachusetts
February 25, 2021

KARUNA THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 53,048	$ 208,929
Investment securities, available-for-sale	269,282	180,468
Prepaid expenses and other current assets	21,864	3,309
Deferred offering costs	405	—
Total current assets	344,599	392,706
Restricted cash	157	123
Property and equipment, net	449	195
Right-of-use lease assets - operating, net	2,420	—
Total assets	$ 347,625	$ 393,024
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable (includes $0 and $51 at December 31, 2020 and 2019, respectively, due to related parties)	$ 865	$ 547
Accrued expenses	5,144	2,353
Current portion of deferred lease obligation	—	58
Current portion of operating lease liability	844	—
Total current liabilities	6,853	2,958
Deferred lease obligation, net of current portion	—	150
Operating lease liability, net of current portion	1,841	—
Total liabilities	8,694	3,108
Commitments and Contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized and 0 shares outstanding at December 31, 2020 and 2019	—	—
Common stock, $0.0001 par value; 150,000,000 shares authorized at December 31, 2020 and 2019; 26,988,458 and 26,012,754 shares issued and outstanding at December 31, 2020 and 2019, respectively	3	3
Additional paid-in capital	482,955	465,420
Accumulated deficit	(144,066)	(75,512)
Accumulated other comprehensive income	39	5
Total stockholders' equity	338,931	389,916
Total liabilities and stockholders' equity	$ 347,625	$ 393,024

The accompanying notes are an integral part of these consolidated financial statements

KARUNA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except share and per share data)

	Year Ended December 31,		
	2020	**2019**	**2018**
Revenue	—	—	—
Operating expenses:			
Research and development	$ 43,408	$ 24,536	$ 11,536
General and administrative	28,408	20,869	2,974
Total operating expenses	71,816	45,405	14,510
Loss from operations	(71,816)	(45,405)	(14,510)
Other income (expense), net:			
Interest income	3,305	2,517	25
Interest income (expense), net (Note 5)	—	11	(407)
Accretion of debt discount (Note 5)	—	(945)	(2,176)
Change in fair value of derivative (Note 5)	—	(135)	(444)
Total other income (expense), net	3,305	1,448	(3,002)
Net loss before income taxes	(68,511)	(43,957)	(17,512)
Income tax provision	(43)	—	—
Net loss attributable to common stockholders	$ (68,554)	$ (43,957)	$ (17,512)
Net loss per share, basic and diluted (Note 8)	$ (2.59)	$ (3.68)	$ (4,378,000)
Weighted average common shares outstanding used in computing net loss per share, basic and diluted	26,446,006	11,958,152	4

The accompanying notes are an integral part of these consolidated financial statements

KARUNA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Year Ended December 31,		
	2020	2019	2018
Net loss	$ (68,554)	$ (43,957)	$ (17,512)
Other comprehensive income:			
Unrealized gains on available-for-sale investments	34	5	—
Comprehensive loss	$ (68,520)	$ (43,952)	$ (17,512)

The accompanying notes are an integral part of these consolidated financial statements

KARUNA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share data)

	Series Seed, A and B Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income	Total Stockholders' Equity (Deficit)
	Shares	Value	Shares	Value				
Balance, December 31, 2017	4,412,500	$ 1	—	$ —	$ 675	$ (14,043)	$ —	$ (13,368)
Issuance of Series A redeemable convertible preferred stock, net of issuance costs of $120	3,126,700	41,964	—	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	958	—	—	958
Exercise of common warrants	—	—	12	—	—	—	—	—
Net loss	—	—	—	—	—	(17,512)	—	(17,512)
Balance, December 31, 2018	7,539,200	$ 41,965	12	$ —	$ 1,633	$ (31,555)	$ —	$ (29,922)
Issuance of Series B redeemable convertible preferred stock, net of issuance costs of $175	5,422,845	81,927	—	—	—	—	—	—
Issuance of common stock upon initial public offering, net of $7,285 in under-writing discounts and commissions and $2,409 in offering costs	—	—	6,414,842	1	93,043	—	—	93,044
Automatic conversion of preferred stock	(12,962,045)	(123,892)	16,833,790	2	123,890	—	—	123,892
Issuance of common stock upon secondary public offering, net of $14,976 in under- writing discounts and commissions and $400 in offering costs	—	—	2,600,000	—	234,224	—	—	234,224
Stock-based compensation expense	—	—	—	—	12,568	—	—	12,568
Exercise of common warrants	—	—	19,986	—	58	—	—	58
Exercise of common options	—	—	38,961	—	4	—	—	4
Vesting of restricted stock units	—	—	105,163	—	—	—	—	—
Other comprehensive income	—	—	—	—	—	—	5	5
Net loss	—	—	—	—	—	(43,957)	—	(43,957)
Balance, December 31, 2019	—	$ —	26,012,754	$ 3	$ 465,420	$ (75,512)	$ 5	$ 389,916
Secondary public offering costs	—	—	—	—	(34)	—	—	(34)
Stock-based compensation expense	—	—	—	—	13,471	—	—	13,471
Exercise of common options	—	—	975,704	—	4,098	—	—	4,098
Other comprehensive income	—	—	—	—	—	—	34	34
Net loss	—	—	—	—	—	(68,554)	—	(68,554)
Balance, December 31, 2020	—	$ —	26,988,458	$ 3	$ 482,955	$ (144,066)	$ 39	$ 338,931

The accompanying notes are an integral part of these consolidated financial statements

KARUNA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2020	**2019**	**2018**
Cash flows from operating activities			
Net loss	$ (68,554)	$ (43,957)	$ (17,512)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	13,471	12,568	958
Amortization of premiums and accretion of discounts on investment securities	642	(824)	—
Depreciation and amortization expense	145	58	6
Loss on disposal of assets	20	—	—
Accretion of debt discount (Note 5)	—	945	2,176
Change in fair value of derivative liability (Note 5)	—	135	444
Non-cash interest (income) expense, net (Note 5)	—	(11)	407
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(18,555)	(1,600)	(1,534)
Change in accrued interest on investment securities	(191)	(436)	—
Accrued expenses	2,791	1,815	105
Accounts payable	318	278	(529)
Right-of-use assets	631	—	—
Operating lease liability	(574)	—	—
Deferred lease obligation	—	106	102
Net cash used in operating activities	(69,856)	(30,923)	(15,377)
Cash flows from investing activities			
Purchases of investment securities	(344,213)	(231,718)	(4,983)
Maturities of investment securities	254,982	50,000	—
Sales of investment securities	—	7,498	—
Acquisition of property and equipment	(419)	(115)	(132)
Net cash used in investing activities	(89,650)	(174,335)	(5,115)
Cash flows from financing activities			
Proceeds from exercise of stock options	4,098	4	—
Payment of offering costs	(405)	—	—
Proceeds from secondary public offering, net of underwriting discounts and commissions	—	234,624	—
Payment of secondary public offering costs	(34)	(400)	—
Proceeds from initial public offering, net of underwriting discounts and commissions	—	95,453	—
Payment of initial public offering costs	—	(2,409)	—
Proceeds from issuance of Series B redeemable convertible preferred stock, net of issuance costs	—	74,825	—
Proceeds from issuance of Series A redeemable convertible preferred stock, net of issuance costs	—	—	15,877
Proceeds from issuance of convertible notes	—	3,128	11,700
Proceeds from exercise of warrant	—	58	—
Net cash provided by financing activities	3,659	405,283	27,577
Net (decrease) increase in cash, cash equivalents and restricted cash	(155,847)	200,025	7,085
Cash, cash equivalents and restricted cash at beginning of period	209,052	9,027	1,942
Cash, cash equivalents and restricted cash at end of period	$ 53,205	$ 209,052	$ 9,027
Supplemental disclosures of cash flows information			
Lease liabilities arising from obtaining right-of-use assets	$ 3,259	$ —	$ —
Conversion of redeemable convertible preferred stock into common stock	$ —	$ 123,892	$ —
Conversion of convertible notes, accrued interest and discount upon conversion to preferred stock	$ —	$ 7,102	$ 26,087

The accompanying notes are an integral part of these consolidated financial statements

Note 1. Nature of the Business

Description of the Business

Karuna Therapeutics, Inc. (the "Company") was incorporated under the laws of the State of Delaware in July 2009 as Karuna Pharmaceuticals, Inc. and is headquartered in Boston, Massachusetts. In March 2019, the Company changed its name to Karuna Therapeutics, Inc. The Company is an innovative clinical-stage biopharmaceutical company driven to create and deliver transformative medicines for people living with psychiatric and neurological conditions.

Since the Company's inception, it has focused substantially all of its efforts and financial resources on organizing and staffing the Company, acquiring and developing its technology, raising capital, building its intellectual property portfolio, undertaking preclinical studies and clinical trials and providing general and administrative support for these activities. The Company has not generated any product revenue related to its primary business purpose to date and is subject to a number of risks similar to those of other early stage companies, including dependence on key individuals, regulatory approval of products, uncertainty of market acceptance of products, competition from substitute products and larger companies, compliance with government regulations, protection of proprietary technology, dependence on third parties, product liability, the impact of the COVID-19 coronavirus pandemic, and the need to obtain adequate additional financing to fund the development of its product candidates.

Forward Stock Split

On June 14, 2019, the Company effected a one-for-1.2987 stock split of its issued and outstanding shares of common stock and a proportional adjustment to the existing conversion ratios for each series of the Company's redeemable convertible preferred stock (see Note 6). Accordingly, all share and per share amounts for all periods presented in the accompanying consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect this stock split and adjustment of the redeemable convertible preferred stock conversion ratios.

Initial Public Offering

On June 27, 2019, the Company's registration statement on Form S-1 relating to its initial public offering of its common stock ("IPO") was declared effective by the Securities and Exchange Commission ("SEC"). In the IPO, which closed on July 2, 2019, the Company issued and sold 6,414,842 shares of common stock, including full exercise of the underwriters' over-allotment option to purchase an additional 836,718 shares, at a public offering price of $16.00 per share. The aggregate net proceeds to the Company from the IPO, inclusive of proceeds from the over-allotment exercise, were approximately $93.0 million after deducting underwriting discounts and commissions of $7.2 million and offering expenses of $2.4 million. Upon closing of the IPO, all 12,962,045 shares of the Company's redeemable convertible preferred stock then outstanding converted into an aggregate of 16,833,790 shares of common stock.

Secondary Public Offering

On November 20, 2019, the Company's registration statement on Form S-1 relating to its secondary public offering of its common stock was declared effective by the SEC. In this offering, which closed on November 25, 2019, the Company issued and sold 2,600,000 shares of common stock at a public offering price of $96.00 per share. The aggregate net proceeds were approximately $234.2 million after deducting underwriting discounts and commissions of $15.0 million and offering expenses of $0.4 million.

Registration Statement and ATM Program

On July 2, 2020, the Company filed an automatically effective registration statement on Form S-3 (the "Registration Statement") with the SEC which registers the offering, issuance and sale of an unspecified amount of common stock, preferred stock, debt securities, warrants and/or units of any combination thereof.

The Company simultaneously entered into an equity distribution agreement with Goldman Sachs & Co. LLC, as sales agent, to provide for the issuance and sale by the Company of up to $150.0 million of common stock from time to time in "at-the-market" offerings under the Registration Statement and related prospectus filed with the Registration Statement (the "ATM Program"). As of December 31, 2020, no sales had been made pursuant to the ATM Program.

Liquidity

The Company's financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities in the ordinary course of business. The Company experienced negative operating cash flows of $69.9 million for the year ended December 31, 2020 and had an accumulated deficit of $144.1 million as of December 31, 2020. The Company expects to continue to generate operating losses for the foreseeable future.

The Company expects that its cash, cash equivalents and available-for-sale investments of $322.3 million as of December 31, 2020 will be sufficient to fund its operating expenses and capital expenditure requirements through at least 12 months from the date of issuance of these consolidated financial statements. The future viability of the Company beyond that point is dependent on its ability to raise additional capital to fund its operations.

If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Note 2. Summary of Significant Accounting Policies

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual of research and development expenses, the valuation of common stock and the associated stock-based awards prior to the Company's IPO, and the valuation of liabilities associated with financial instruments and derivatives. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company's estimates.

The consolidated financial statements include the accounts of Karuna Therapeutics, Inc. and its wholly owned subsidiary, Karuna Securities Corporation. All inter-company transactions and balances have been eliminated in consolidation.

Cash and Cash Equivalents

The Company considers all short-term, highly liquid investments with maturities of 90 days or less at acquisition date to be cash equivalents.

Investment Securities

The Company's investment securities are classified as available-for-sale and are carried at fair value with the unrealized gains and losses reported as a component of accumulated other comprehensive income (loss) in stockholders' equity. The cost of investment securities classified as available-for-sale is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization and accretion are included in interest income. Realized gains and losses are included as a component of other income (expense), net based on the specific identification method.

When the fair value of an available-for-sale debt security falls below the amortized cost basis it is evaluated to determine if any of the decline in value is attributable to credit loss. Decreases in fair value attributable to credit loss are recorded directly to earnings with a corresponding allowance for credit losses, limited to the amount that the fair value is less than the amortized cost basis. If the credit quality subsequently improves the allowance is reversed up to a maximum of the previously recorded credit losses. When the Company intends to sell an impaired available-for-sale debt security, or if it is more likely than not that the Company will be required to sell the security prior to recovering the amortized cost basis, the entire fair value adjustment will immediately be recognized in earnings with no corresponding allowance for credit losses.

Concentration of Manufacturing Risk

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Deferred Offering Costs

The Company capitalizes certain legal, professional accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in stockholders' equity (deficit) as a reduction of additional paid-in capital generated as a result of the offering. Should the in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the statement of operations. Deferred offering costs were approximately $0.4 million as of December 31, 2020. As of December 31, 2019 and 2018, there were no deferred offering costs outstanding. All deferred offering costs accumulated during 2019 and associated with the Company's IPO and secondary public offering were recorded as a reduction of additional paid-in capital upon the close of the Company's public offerings on July 2, 2019 and November 25, 2019, respectively.

Fair Value of Financial Instruments

The Company's financial instruments consist of cash equivalents, investment securities, accounts payable, accrued expenses, convertible notes and derivatives embedded within the convertible notes. The carrying amount of accounts payable, accrued expenses and convertible notes are considered a reasonable estimate of their fair value, due to the short-term maturity of these instruments. The Company's cash equivalents, investment securities and derivative liabilities are carried at fair value, determined according to the fair value hierarchy described below (see Note 10).

The Company follows the guidance in FASB ASC 820, *Fair Value Measurements and Disclosures*, which defines fair value and establishes a fair value hierarchy that prioritizes the inputs to valuation techniques used to measure fair value. The hierarchy gives the highest priority to unadjusted quoted prices in active markets for identical assets or liabilities (Level 1 measurements) and the lowest priority to unobservable inputs (Level 3 measurements). The three levels of the fair value hierarchy are described below:

Level 1: Quoted prices (unadjusted) in active markets for identical assets or liabilities that the reporting entity has the ability to access at the measurement date.

Level 2: Valuations based on quoted prices in markets that are not active or for which all significant inputs are observable, either directly or indirectly.

Level 3: Prices or valuations that require inputs that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Fair value is a market-based measure considered from the perspective of a market participant rather than an entity-specific measure. Therefore, even when market assumptions are not readily available, the Company's own assumptions reflect those that market participants would use in pricing the asset or liability at the measurement date. The Company uses prices and inputs that are current as of the measurement date, including during periods of market dislocation. In periods of market dislocation, the observability of prices and inputs may be reduced for many instruments. This condition could cause an instrument to be reclassified from Level 1 to Level 2 or Level 2 to Level 3.

Property and Equipment

Property and equipment are recorded at cost and depreciated over their estimated useful lives using the straight-line method. Leasehold improvements are amortized over the shorter of their estimated useful lives or the term of the lease by use of the straight-line method. Maintenance and repair costs are expensed as incurred. When assets are retired or sold, the assets and accumulated depreciation are removed from the respective accounts and any gain or loss is recognized.

Convertible Notes and Derivative Liabilities

In connection with the issuance of the Wellcome Trust Convertible Notes and the Convertible Notes (see Note 5), the Company had identified embedded derivatives, which were recorded as liabilities on the Company's balance sheet and were remeasured to fair value at each reporting date until the derivative was settled. Changes in the fair value of the derivative liabilities were recognized as change in fair value of derivative in the statements of operations. The fair value of the derivative liabilities were determined at each period end using a with and without method, which assesses the likelihood and timing of events that would result in either a conversion or change-of-control feature being triggered, as well as changes in the market conditions.

Upon issuance of the notes, each note was recorded at cost, net of the derivative liability. The discount on each note was amortized as interest expense to the date such note was expected to convert using the effective interest rate method and was reflected in the statements of operations as accretion of debt discount.

The Company classified its derivative liabilities in the balance sheet as current or non-current based on its expectation of when the derivative will be settled, consistent with the assumptions used when determining the fair value of the derivative liabilities.

In 2019, all notes were converted into redeemable convertible preferred stock and the associated derivative liabilities were settled in connection with the Company's issuance of Series B redeemable convertible preferred stock. There were no convertible notes or derivative liabilities outstanding as of December 31, 2020 and 2019.

Redeemable Convertible Preferred Stock

Prior to the IPO, the Company recorded all shares of redeemable convertible preferred stock at their respective fair values on the dates of issuance, net of issuance costs. The redeemable convertible preferred stock was recorded outside of permanent equity because upon the occurrence of certain deemed liquidation events, the majority of the holders could opt to redeem the shares at the liquidation preference and these events, including a merger, acquisition or sale of substantially all of the assets, was considered not solely within the Company's control. Prior to the IPO, the Company had not adjusted the carrying values of the redeemable convertible preferred stock to its redemption value because it was uncertain whether or when a deemed liquidation event would occur. Upon closing of the IPO, all 12,962,045 shares of the Company's redeemable convertible preferred stock then outstanding converted into an aggregate of 16,833,790 shares of common stock.

Leases

Effective January 1, 2020, the Company adopted ASU 2016-02, *Leases (Topic 842),* ("ASU 2016-02" or "ASC 842"), using the modified retrospective transition approach and utilizing the effective date as the date of initial application. As a result, prior periods are presented in accordance with the previous guidance in ASC 840, *Leases* ("ASC 840").

At the inception of an arrangement, we determine whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Operating leases are recognized on the balance sheet as right-of-use ("ROU") lease assets, current portion of operating lease liability, and operating lease liability, net of current portion. We do not have financing leases.

Operating lease liabilities and their corresponding ROU lease assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the ROU lease asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, we utilize our incremental borrowing rate to discount lease payments, which reflects the fixed rate at which we could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. To estimate our incremental borrowing rate, a credit rating applicable to us is estimated using a synthetic credit rating analysis since we do not currently have a rating agency-based credit rating. Prospectively, we will adjust the ROU lease assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

We have elected not to recognize leases with an original term of one year or less on the balance sheet. We typically only include an initial lease term in our assessment of a lease arrangement. Options to renew a lease are not included in our assessment unless there is reasonable certainty that we will renew.

Assumptions that we made at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. Lease modifications are accounted for as a separate contract or are treated as a change in accounting for the existing lease. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include salaries and bonuses, stock-based compensation, employee benefits, consulting costs and external contract research and development and manufacturing expenses.

Upfront payments and milestone payments made for the licensing of technology are expensed as research and development in the period in which they are incurred. Advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Research and Development Contract Costs and Accruals

The Company accrues for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of discovery and preclinical studies, clinical trials, and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated amount of services provided and includes these costs in accrued liabilities in the balance sheets and within research and development expense in the statements of operations. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the research studies or clinical trials and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Stock-Based Compensation

The Company measures all stock options and other stock-based awards to employees, directors and non-employees based on the fair value on the date of the grant and recognizes compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. The Company has mainly issued stock options with service-based vesting conditions and records the expense for these awards using the straight-line method. The Company has also issued stock options with performance-based vesting conditions and records the expense for these awards at the time that the achievement of the performance becomes highly probable or complete. The Company recognizes adjustments to stock-based compensation expense for forfeitures as they occur. The Company classifies stock-based compensation expense in its statements of operations in the same manner in which the award recipient's payroll costs are classified or in which the award recipients' service payments are classified.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model. The Company had historically been a private company and lacks company-specific historical and implied volatility information. Therefore, expected stock volatility has been calculated based on the historical volatility of a publicly traded set of peer companies. The Company expects to continue to use such methodology until such time as it has adequate historical data regarding the volatility of its own publicly traded stock price.

The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The fair value for each restricted common stock award is estimated on the date of grant based on the fair value of the Company's common stock on that same date.

Net Loss Per Share

In July 2019, upon closing of the IPO, all outstanding shares of the Company's redeemable convertible preferred stock automatically converted to common stock. Prior to this conversion, the Company followed the two-class method when computing net income (loss) per share, as the Company had issued shares that met the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income

available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) attributable to common stockholders is computed by adjusting income (loss) attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities, including outstanding stock options. Diluted net income (loss) per share attributable to common stockholders is computed by dividing the diluted net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of outstanding stock options.

Prior to the IPO, the Company's outstanding redeemable convertible preferred stock contractually entitled the holders of such shares to participate in distributions but contractually did not require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

The Company reported a net loss attributable to common stockholders for the years ended December 31, 2020, 2019 and 2018.

Comprehensive Income (Loss)

Comprehensive income (loss) includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2020 and 2019, the Company's only element of other comprehensive income (loss) was unrealized gains on available-for-sale investments.

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*, which replaces the existing guidance in ASC 840, "Leases". Topic 842 was subsequently amended by ASU 2018-11, *Leases (Topic 842): Targeted Improvements*, and ASU 2019-01, *Leases (Topic 842): Codification Improvements*. The new leasing standard generally requires lessees to recognize operating and financing lease liabilities and corresponding ROU assets on the consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. The Company adopted the new standard effective January 1, 2020 and did not restate comparative periods. The Company elected the package of practical expedients permitted under the transition guidance and as such, the adoption of this ASU did not change the classification of any of our existing leases. The Company elected to combine lease and non-lease components, elected not to record leases with an initial term of 12 months or less on the balance sheet and recognized the associated lease payments in the consolidated statements of operations on a straight-line basis over the lease term. As of January 1, 2020, the Company recognized $1.5 million as total lease liabilities and $1.2 million as total ROU lease assets on its consolidated balance sheet as a result of the adoption. The deferred lease obligation of $0.2 million outstanding as of December 31, 2019 was recorded as a reduction of the ROU lease asset.

In August 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820)*. ASU 2018-13 modifies fair value disclosure requirements, specifically around level transfers and valuation of Level 3 assets and liabilities. ASU 2018-13 is effective for financial statements issued for annual and interim periods beginning after December 15, 2019 for all entities. Early adoption of all or part of ASU 2018-13 is permitted. Effective January 1, 2020, the Company adopted the standard. The adoption did not have a material impact on the Company's consolidated financial statements.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*. The new standard simplifies the accounting for income taxes by removing certain exceptions within the guidance and making various other amendments. ASU 2019-12 is effective for financial statements issued for annual and interim periods beginning after December 15, 2020. Early adoption is permitted, including adoption in any interim period for which financial statements have not yet been issued. An entity that elects to early adopt in an interim period should reflect any adjustments as of the beginning of the annual period that includes that interim period. In addition, an entity that early adopts must adopt all amendments of ASU 2019-12 in the same period and apply each amendment on either a retrospective or modified-retrospective basis as applicable. Effective January 1, 2020, the Company elected to early adopt the standard. The adoption did not have a material impact on the Company's consolidated financial statements.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326)*. The new standard adjusts the accounting for assets held at amortized cost basis, including marketable securities accounted for as available for sale. The standard eliminates the probable initial recognition threshold and 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. Under this ASU, the standard is effective for public business entities, excluding entities eligible to be smaller reporting companies as defined by the SEC, for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. For all other entities, the standard is effective for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. As of January 1, 2021, the Company no longer qualified as a smaller reporting company for filing purposes, and therefore adopted ASU 2016-13 effective January 1, 2020. The adoption did not have a material impact on the Company's consolidated financial statements.

In November 2018, the FASB issued ASU 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*. The amendments in this update clarify that certain transactions between collaborative arrangement participants should be accounted for as revenue under ASC 606, *Revenue from Contracts with Customers* when the counter party is a customer in the context of a unit of account. This update also precludes companies from presenting transactions with collaborative partners that are outside the scope of Topic 606 together with revenue within the scope of Topic 606. For public business entities, ASU 2018-18 is effective for fiscal years beginning after December 31, 2019, and interim periods within those fiscal years. Effective January 1, 2020, the Company adopted the standard. The adoption did not have a material impact on the Company's consolidated financial statements.

In August 2018, the FASB issued ASU 2018-15, *Intangibles-Goodwill and Other-Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*. The amendments in this update align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use software license). The accounting for the service element of a hosting arrangement that is a service contract is not affected by the amendments in this update. For public business entities, ASU 2018-15 is effective for fiscal years beginning after December 31, 2019, and interim periods within those fiscal years. The adoption did not have a material impact on the Company's consolidated financial statements.

Note 3. Property and Equipment, Net

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

	December 31,	
	2020	2019
Computer equipment	$ 229	$ 87
Leasehold improvements	154	115
Software	154	38
Furniture and fixtures	85	10
Office equipment	29	2
Total property and equipment	651	252
Less: accumulated depreciation	(202)	(57)
Property and equipment, net	$ 449	$ 195

Depreciation expense was $0.1 million for the year ended December 31, 2020 and less than $0.1 million for the years ended December 31, 2019 and 2018.

Note 4. Prepaid Expenses and Other Current Assets and Accrued Expenses

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

	December 31,	
	2020	2019
Prepaid research and development expenses	$ 18,660	$ 694
Prepaid insurance	2,116	2,130
Other	1,088	485
Total prepaid expenses and other current assets	$ 21,864	$ 3,309

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2020	2019
Accrued payroll and related expenses	$ 2,654	$ 1,823
Accrued research and development expenses	1,829	344
Professional fees	458	142
Other	203	44
Total accrued expenses	$ 5,144	$ 2,353

Note 5. Convertible Notes Payable

Wellcome Trust Convertible Notes

In July 2015, the Company entered into a Company Funding Agreement with The Wellcome Trust, Limited (“Wellcome Trust”), pursuant to which the Company was eligible to receive $3.8 million in gross proceeds upon the achievement of specified milestones (the “2015 Convertible Note”). As of December 31, 2017, the Company had received the full amount of gross proceeds under the 2015 Convertible Note.

In June 2018, the Company entered into a second Company Funding Agreement with Wellcome Trust to receive up to $8.0 million in gross proceeds from the issuance of a convertible note (the “2018 Convertible Note,” and together with the 2015 Convertible Note, the “Wellcome Trust Notes”). The Company received

$2.0 million of proceeds in July 2018, $2.7 million in November 2018, $1.6 million in March 2019, and $1.6 million in April 2019.

The Wellcome Trust Notes have a stated interest rate of 2% per annum above the three-month Dollar LIBOR rate, which was not payable until settlement of the principal. The notes were subject to redemption upon written demand by Wellcome Trust any time after the fifth anniversary of the effective date. The principal due under the Wellcome Trust Notes was convertible into the class of the Company's stock issued in the Company's next qualified financing or upon event of default at a discounted conversion price between 0% and 25% of the purchase price per share of such securities issued. The accrued interest in such a circumstance would be forgiven.

At inception of each the 2015 Convertible Note and 2018 Convertible Note, the Company concluded that the each contained a conversion option at a significant discount that was deemed to be an embedded derivative, which was required to be bifurcated and accounted for separately from the debt host. There were no debt issuance costs associated with the 2018 Convertible Note.

The Company recognized the following changes in the debt related to the Wellcome Trust Notes during the years ended December 31, 2019 and 2018 (in thousands):

		Financial statement impacted
Balance, December 31, 2017	$ 3,985	
Issuance of 2018 Convertible Note	2,000	Balance sheet
Accretion to settlement value	51	Statement of operations
Accrued interest	102	Statement of operations
Interest forgiven upon conversion	(289)	Statement of operations
Conversion of Wellcome Trust Notes to redeemable convertible preferred stock	(5,849)	Balance sheet
Balance, August 1, 2018 (date of conversion)	—	
Issuance of 2018 Convertible Note	2,700	Balance sheet
Allocation of proceeds to derivative liability	(375)	Balance sheet
Accretion to settlement value	180	Statement of operations
Accrued interest	11	Statement of operations
Balance, December 31, 2018	2,516	
Issuance of 2018 Convertible Note	3,128	Balance sheet
Allocation of proceeds to derivative liability	(750)	Balance sheet
Accretion to settlement value	945	Statement of operations
Accrued interest	29	Statement of operations
Interest forgiven upon conversion	(40)	Statement of operations
Conversion of Wellcome Trust Notes to redeemable convertible preferred stock	(5,828)	Balance sheet
Balance, December 31, 2019	$ —	

There were no debt issuances outstanding under the Wellcome Trust Notes as of December 31, 2019 or issued during the year ended December 31, 2020.

Convertible Notes

Since inception, and excluding the Wellcome Trust Notes, the Company has issued $14.0 million of convertible notes (the "Convertible Notes"), of which $13.5 million were issued to PureTech Health LLC ("PureTech Health"), a related party (see Note 13). During the year ended December 31, 2018, the Company issued Convertible Notes to PureTech Health with principal totaling $7.0 million. There were no debt issuance costs associated with the Convertible Notes.

The Convertible Notes had a stated interest rate of 10% per annum which is not payable until the settlement of the principal. The notes matured upon written demand by the majority note holders. In the event of a default, the interest rate was 15% per annum. Principal and unpaid interest due under the notes convert on demand of a majority of note holders into the class of the Company's stock issued in the Company's next qualified financing at a conversion price between 0% to 25% discount off of the purchase price per share of such securities issued.

The Company concluded that the Convertible Notes contained a conversion option at a significant premium that was deemed to be an embedded derivative, which is required to be bifurcated and accounted for separately from the debt host.

In August 2018, the outstanding Convertible Notes were converted into Series A Preferred Stock.

The Company recognized the following changes in the debt related to the Convertible Notes during the year ended December 31, 2018 (in thousands):

			Financial statement impacted
Balance, December 31, 2017	$	7,674	
Issuance of new notes		7,000	Balance sheet
Allocation of proceeds to derivative liability		(1,418)	Balance sheet
Accretion to settlement value		1,945	Statement of operations
Accrued interest		630	Statement of operations
Interest forgiven upon conversion		(47)	Statement of operations
Conversion of Convertible Notes to redeemable convertible preferred stock		(15,784)	Balance sheet
Balance, December 31, 2018	$	—	

There were no debt issuances outstanding under the Convertible Notes as of December 31, 2018 or issued during the years ended December 31, 2020 and 2019.

Note 6. Redeemable Convertible Preferred Stock

Series Seed Redeemable Convertible Preferred Stock

Between 2009 and 2011, the Company authorized and issued 4,412,500 shares of Series Seed Preferred Stock at an issuance price of $0.0001 per share, for total proceeds of less than $0.1 million.

There were no issuance costs in connection with the Series Seed Preferred Stock issuance.

Series A Redeemable Convertible Preferred Stock

In August 2018, the Company authorized 3,126,700 shares of Series A Preferred Stock. The Company then issued 1,188,707 shares of Series A Preferred Stock at an issuance price of $13.46 per share resulting in gross proceeds of approximately $16.0 million. There were $0.1 million of issuance costs associated with the Series A Preferred Stock.

In conjunction with the August 2018 issuance of Series A Preferred Stock, all outstanding principal and accrued interest under the Wellcome Trust Notes and Convertible Notes converted into 1,937,993 shares of Series A Preferred Stock.

Series B Redeemable Convertible Preferred Stock

In March 2019, the Company authorized 5,422,845 shares of Series B Preferred Stock. The Company then issued 4,953,758 shares of Series B Preferred Stock at an issuance price of $15.14 per share resulting in gross proceeds of approximately $75.0 million. There were $0.2 million of issuance costs associated with the Series B Preferred Stock.

In conjunction with the March 2019 issuance of Series B Preferred Stock, all outstanding principal and accrued interest under the Wellcome Trust Notes converted into 331,344 shares of Series B Preferred Stock. In April 2019, the Company received an additional $1.6 million pursuant to the 2018 Convertible Note which was subsequently converted into 137,743 shares of Series B Preferred Stock.

Upon closing of the Company's IPO, the then-outstanding shares of the Series Seed, Series A and Series B redeemable convertible preferred stock converted into common stock. As of December 31, 2020 and 2019, there were no shares of redeemable convertible preferred stock authorized, issued or outstanding.

Note 7. Stockholders' Equity

Preferred Stock

On July 2, 2019, in connection with the closing of the Company's IPO, the Company filed its restated Certificate of Incorporation, which authorizes the Company to issue up to 10,000,000 shares of preferred stock, $0.0001 par value per share. There were no shares of preferred stock outstanding as of December 31, 2020 or 2019.

Common Stock

As of December 31, 2020, the Company's Certificate of Incorporation authorized the Company to issue 150,000,000 shares of common stock, $0.0001 par value per share.

Holders of the common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings. The holders of common stock shall be entitled to receive dividends out of funds legally available, as declared by the board of directors. These dividends are subject to the preferential dividend rights of the holders of the Company's preferred stock. Through December 31, 2020, no cash dividends have been declared or paid.

Upon completion of the Company's IPO on July 2, 2019, all outstanding shares of Series Seed, Series A, and Series B redeemable convertible preferred stock converted to common stock.

As of December 31, 2020, there were 26,988,458 shares of common stock outstanding.

Note 8. Net Loss per Share

Net Loss per Share

The following table sets forth the computation of basic and diluted net loss per share of common stock for the years ended December 31, 2020, 2019 and 2018 (in thousands, except share and per share data):

	Year Ended December 31,		
	2020	2019	2018
Net Loss	$ (68,554)	$ (43,957)	$ (17,512)
Weighted-average shares used in computing net loss per share	26,446,006	11,958,152	4
Net loss per share, basic and diluted	$ (2.59)	$ (3.68)	$ (4,378,000)

The Company's potentially dilutive securities, which include stock options and convertible preferred stock, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same.

Prior to the IPO, the Company's outstanding shares of preferred stock contractually entitled the holders of such shares to participate in distributions but contractually did not require the holders of such shares to participate in losses of the Company. Accordingly, these shares have not been included in the denominator used to calculate net loss per share.

Common Stock Equivalents

The following common stock equivalents presented based on amounts outstanding at each period end, have been excluded from the calculation of diluted net loss per share because including them would have had an anti-dilutive impact:

	December 31,		
	2020	**2019**	**2018**
Redeemable convertible preferred stock (as converted to common stock)	—	—	9,791,151
Stock options to purchase common stock	4,612,790	4,614,544	2,310,369
Warrants to purchase common stock	—	—	19,986
	4,612,790	4,614,544	12,121,506

Note 9. Stock-based Compensation

Stock Options

In September 2009, the Company's board of directors approved the 2009 Stock Incentive Plan (the "2009 Plan") which provided for the grant of incentive stock options to employees and non-statutory stock options to directors, consultants, and non-employees of the Company. The aggregate common shares issuable were 3,911,138 under the 2009 Plan, as amended. The 2009 Plan terminated in July 2019 effective upon the completion of the Company's IPO. No additional options will be granted under the 2009 Plan. At December 31, 2020, there were 2,660,816 options and restricted stock units ("RSUs") outstanding under the 2009 Plan.

In May 2019, the board of directors approved the 2019 Stock Option and Incentive Plan (the "2019 Plan") which became effective on June 26, 2019, the date immediately prior to the date on which the registration statement related to the IPO was declared effective by the SEC. The 2019 Plan will expire in May 2029. Under the 2019 Plan, the Company may grant incentive stock options, non-statutory stock options, restricted stock awards, RSUs and other stock-based awards. There were 1,709,832 shares of the Company's common stock initially reserved for issuance under the 2019 Plan. The number of shares of common stock underlying awards that expire, or are terminated, surrendered, canceled or forfeited without having been fully exercised under the 2009 Plan will be added to the shares of common stock available for issuance under the 2019 Plan. In addition, the number of shares available for issuance automatically increases on January 1 of each calendar year, commencing on January 1, 2020, by 4% of the number of shares of common stock outstanding on the immediately preceding December 31 or such lesser amount determined by the Company's board of directors or the compensation committee of the board of directors. As of December 31, 2020, there were 934,730 common shares available for issuance and 1,951,974 options outstanding under the 2019 Plan.

Options under the 2019 Plan generally vest based on the grantee's continued service with the Company during a specified period following a grant as determined by the board of directors and expire ten years from the grant date. In general, awards typically vest in four years, but vesting conditions can vary based on the discretion of the Company's board of directors.

A summary of the Company's stock option activity and related information is as follows:

	Number of Shares	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2019	4,614,544	$ 8.94	8.3	$ 306,395
Granted	1,029,950	93.33		
Exercised	(975,704)	4.20		
Forfeited	(56,000)	21.77		
Outstanding as of December 31, 2020	4,612,790	$ 28.63	8.3	$ 336,740
Options vested and expected to vest as of December 31, 2020	4,612,790	$ 28.63	8.3	$ 336,740
Options exercisable as of December 31, 2020	2,858,905	$ 10.48	7.9	$ 260,485

The aggregate intrinsic values of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the publicly traded stock price of the Company's common stock as of December 31, 2020.

As of December 31, 2020, there was $46.1 million of unrecognized compensation cost, which is expected to be recognized over a weighted-average period of 3.04 years.

The fair value of all option activity was estimated at the date of grant using the Black-Scholes model with the following assumptions:

	Year Ended December 31,		
	2020	2019	2018
Fair value of options	$ 35.17 - 59.72	$ 3.84 - 8.05	$ 4.49 - 5.49
Fair value of common stock	$ 62.14 - 106.46	$ 9.20 - 20.02	$ 9.14 - 9.44
Expected term (in years)	5.50 - 7.00	5.02 - 6.16	5.65 - 9.34
Expected volatility	55.73% - 61.28%	43.54% - 48.22%	45.57% - 48.84%
Risk-free interest rate	0.35% - 1.49%	1.59% - 2.44%	2.69% - 3.04%
Expected dividend yield	0.00%	0.00%	0.00%

On May 16, 2019, the Company issued 105,163 fully vested restricted common stock units. The average grant date fair value was $10.97 per share. As of December 31, 2020 and 2019, there was no unrecognized compensation expense related to unvested RSUs.

Warrants

In October 2016, PureTech Health, a related party, agreed to provide management services to the Company in exchange for a warrant to purchase up to 19,998 shares of the Company's common stock. The warrant vested monthly as services were performed over a 24-month period and had a purchase price of $2.92 per share. The total expense for the year ended December 31, 2018 for the warrant was less than $0.1 million, and no expense was recognized in the years ended December 31, 2020 and 2019, as the warrant was fully vested as of October 2018. There was no unrecognized compensation cost related to the warrants as of December 31, 2020, 2019 and 2018.

In August 2018, PureTech Health partially exercised the warrant to purchase 12 shares of the Company's common stock, resulting in a nominal amount of proceeds to the Company. In March 2019, PureTech Health

exercised the remaining portion of the warrant to purchase 19,986 shares of the Company's common stock, resulting in proceeds to the Company of $0.1 million. There were no outstanding warrants as of December 31, 2020 or 2019.

Stock-based Compensation Expense

Stock-based compensation expense is classified in the statements of operations for the years ended December 31, 2020, 2019 and 2018 as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Research and development	$ 3,767	$ 580	$ 107
General and administrative	9,704	11,988	851
Total stock-based compensation expense	$ 13,471	$ 12,568	$ 958

Note 10. Fair Value of Financial Assets and Liabilities

The following table presents information about the Company's assets as of December 31, 2020 and 2019 that are measured at fair value on a recurring basis and indicates the level of the fair value hierarchy utilized to determine such fair values (in thousands):

	Fair Value Measurement at December 31, 2020 Using			
	Level 1	Level 2	Level 3	Total
Cash equivalents:				
Money market fund	$ 50,141	$ —	$ —	$ 50,141
Investment securities:				
US Treasuries	172,295	—	—	172,295
Corporate debt securities	—	36,817	—	36,817
Commercial paper	—	60,170	—	60,170
Total	$ 222,436	$ 96,987	$ —	$ 319,423

	Fair Value Measurement at December 31, 2019 Using			
	Level 1	Level 2	Level 3	Total
Cash equivalents:				
Money market fund	$ 197,303	$ —	$ —	$ 197,303
Investment securities:				
US Treasuries	180,468	—	—	180,468
Total	$ 377,771	$ —	$ —	$ 377,771

The fair values of the Company's commercial paper and corporate debt securities are based on prices obtained from independent pricing sources. Securities with validated quotes from pricing services are reflected within Level 2, as they are primarily based on observable pricing for similar assets or other market observable inputs. Typical inputs used by these pricing services include, but are not limited to, reported trades, benchmark yields, issuer spreads, bids, offers or estimates of cash flow, prepayment spreads and default rates.

The Company does not hold any securities classified as Level 3, which are securities valued using unobservable inputs. The Company has not transferred any investment securities between the classification levels.

The estimated fair value and amortized cost of the Company's available-for-sale investments, by contractual maturity and security type, are summarized as follows (in thousands):

	December 31, 2020			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
US Treasuries (due within one year)	$ 172,265	$ 37	$ (7)	$ 172,295
Corporate debt securities (due within one year)	36,823	3	(9)	36,817
Commercial paper (due within one year)	60,155	16	(1)	60,170
Total	$ 269,243	$ 56	$ (17)	$ 269,282

	December 31, 2019			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
US Treasuries (due within one year)	$ 180,463	$ 5	$ —	$ 180,468
Total	$ 180,463	$ 5	$ —	$ 180,468

The Company classifies all of its available-for-sale investment securities, including those with maturities beyond one year, as current assets on its consolidated balance sheets based on the highly liquid nature of the investment securities and because these investment securities are considered available for use in current operations.

As described under Recently Adopted Accounting Pronouncements (see Note 2) the Company adopted FASB ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326)* as of January 1, 2020. The new standard requires the Company to determine whether a decline in the fair value below the amortized cost basis of available-for-sale securities is due to credit-related factors. At each reporting date, the Company performs an evaluation of impairment to determine if any unrealized losses are the result of credit losses. Impairment is assessed at the individual security level. Factors considered in determining whether a loss resulted from a credit loss or other factors include the Company's intent and ability to hold the investment until the recovery of its amortized cost basis, the extent to which the fair value is less than the amortized cost basis, the length of time and extent to which fair value has been less than the cost basis, the financial condition of the issuer, any historical failure of the issuer to make scheduled interest or principal payments, any changes to the rating of the security by a rating agency, any adverse legal or regulatory events affecting the issuer or issuer's industry, and any significant deterioration in economic conditions.

Unrealized losses on available-for-sale securities presented in the previous table have not been recognized in the consolidated statements of operations because the securities are high credit quality, investment grade securities that the Company does not intend to sell and will not be required to sell prior to their anticipated recovery, and the decline in fair value is attributable to factors other than credit losses. Based on its evaluation, the Company determined its year-to-date credit losses related to its available-for-sale securities were immaterial at December 31, 2020.

The derivative liability was considered a Level 3 liability because its fair value measurement was based, in part, on significant inputs not observed in the market. The Company recognized the following changes in the fair value of derivative liabilities during the years ended December 31, 2019 and 2018 (in thousands):

Balance, December 31, 2017	$	2,606
Allocation of note issuance proceeds to derivative		1,418
Change in fair value of derivative		430
Conversion of convertible debt to Series A preferred stock		(4,454)
Balance, August 1, 2018 (date of conversion)		—
Allocation of note issuance proceeds to derivative		375
Change in fair value of derivative		14
Balance, December 31, 2018		389
Allocation of note issuance proceeds to derivative		750
Change in fair value of derivative		135
Conversion of convertible debt to Series B preferred stock		(1,274)
Balance, December 31, 2019	$	—

There was no derivative liability recorded as of December 31, 2020 or 2019.

Note 11. Commitments and Contingencies

Leases

The Company entered into an agreement to lease approximately 7,050 square feet of office space in Boston, Massachusetts (“Original Premises”) that began in December 2018 and had an original expiry in February 2023. In January 2020, the Company entered into an amended agreement (“Amended Lease Agreement”) to gain access to approximately 4,175 square feet of additional office space (“Expansion Premises”) beginning in March 2020, and to extend the maturity of the agreement for the Original Premises to December 2023. The Amended Lease Agreement provides for future minimum annual rental payments as defined within the agreement. Under the terms of the amended agreement, the Company is required to maintain a cash balance of approximately $0.2 million to secure a letter of credit associated with this lease. The amount was classified as restricted cash in the consolidated balance sheets as of December 31, 2020 and 2019. The Amended Lease Agreement also provides for approximately $0.1 million in leasehold incentives which may be applied to base rent or improvements to the Expansion Premises, subject to limitations.

The Company determined the Amended Lease Agreement represented a lease modification, and the Original Premises and Expansion Premises were identified as separate lease components. The extension of maturity with respect to the Original Premises was treated as a modification not accounted for as a separate contract, in which the lease classification was reassessed and the lease liability was remeasured. The effect of the remeasurement, in the amount of $0.4 million, was recorded as an adjustment to the right-of-use asset as of February 1, 2020, the effective date of the modification. The addition of the Expansion Premises was accounted for as a separate contract which granted the Company an additional right of use not included in the original lease, in which the lease payments increased commensurate with the standalone price for the additional right of use. As the leasehold incentives were not paid or payable at commencement, the Company will account for the incentives once the contingency is resolved.

In February 2020, the Company entered into an agreement to lease approximately 5,050 square feet of office space, and furniture within the office space, in Carmel, Indiana (“Indiana Lease Agreement”), which began in June 2020 and expires in July 2023, with the option to renew for an additional three-year term. In addition, the agreement provides an option to purchase the office furniture at the expiration of the agreement.

The office space and office furniture within the Indiana Lease Agreement were each determined to represent separate lease components. Consideration for the contract was allocated to each lease component based on their relative stand-alone selling price. The options to renew the lease for an additional three-year

term as well as purchase the office furniture at the expiration of the agreement were excluded from the determination of lease liabilities arising from obtaining the ROU assets, as they were not considered probable of being exercised at commencement.

For each of the lease agreements entered into or modified, the Company identified certain non-lease components. Lease and non-lease components were combined into a single lease component. In addition, all identified leases were assessed as operating leases.

As the Company's leases do not provide an implicit rate, the Company used its incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a term equal to the lease payments in a similar economic environment in determining the present value of lease payments for each identified lease at the lease commencement date.

In addition to the lease liabilities arising from ROU assets recognized upon adoption of ASC 842, *Leases* (see Note 2), the Company recognized approximately $1.8 million in incremental lease liabilities arising from obtaining ROU assets as a result of the Amended Lease Agreement and Indiana Lease Agreement.

The components of lease cost were as follows (dollar amounts in thousands):

	Year Ended December 31,		
	2020	2019	2018
Lease Cost			
Operating lease cost	$ 791	$ 441	$ 37
Short-term lease cost	—	—	—
Total lease cost	$ 791	$ 441	$ 37

As the Company adopted ASC 842 effective January 1, 2020, prior period amounts have not been adjusted and continue to be reported in accordance with the Company's historic accounting under Topic 840.

	Year Ended December 31, 2020
Other Information	
Cash paid for amounts included in the measurement of lease liabilities	$ 733
Operating lease liabilities arising from obtaining right-of-use assets	$ 3,259
Weighted-average remaining lease term	2.94 years
Weighted-average discount rate	6.21%

The following is a maturity analysis of the annual undiscounted cash flows of the operating lease liabilities and a reconciliation to present value of lease liabilities as of December 31, 2020 (in thousands):

Year ended:	
December 31, 2021	982
December 31, 2022	1,001
December 31, 2023	949
Total future minimum lease payments	2,932
Less imputed interest	(246)
Present value of lease liabilities	$ 2,686

Future minimum lease payments under non-cancelable operating lease agreements as of December 31, 2019 (under ASC 840, prior to the adoption of ASC 842 effective January 1, 2020), were as follows (in thousands):

Year ended:		
December 31, 2020	$	499
December 31, 2021		506
December 31, 2022		514
December 31, 2023		86
December 31, 2024 and thereafter		—
	$	1,605

Intellectual Property License with Eli Lilly and Company

In May 2012, the Company entered into an exclusive license agreement (the “Lilly License Agreement”) with Eli Lilly, pursuant to which Eli Lilly assigned to the Company all of its rights to certain patents (now expired), regulatory documentation, data records and materials related to xanomeline. The Company is also entitled to sublicense or otherwise transfer the rights granted in connection with the Lilly License Agreement.

Under the Lilly License Agreement, the Company is obligated to use commercially reasonable efforts to develop, manufacture, commercialize and seek and maintain regulatory approval for xanomeline, in any formulation, for use in humans.

The Company paid Eli Lilly an upfront payment of $0.1 million and has agreed to make milestone payments to Eli Lilly of up to an aggregate of $16 million upon the achievement of specified regulatory milestones and up to an aggregate of $54 million in commercial milestones. In addition, the Company is obligated to pay Eli Lilly tiered royalties, at rates in the low to mid single-digit percentages, on the worldwide net sales of any commercialized product on a country-by-country basis until the expiration of the applicable royalty term, which is the longer of six years from the date of first commercial sale of each licensed product within a country or data exclusivity in such country. During the royalty term, Eli Lilly is prohibited from granting any third-party rights to the patents, regulatory documentation, data records and materials that have been licensed to the Company under the Lilly License Agreement.

The Lilly License Agreement will expire on the later of (i) the expiration of the last-to-expire royalty term on a licensed product-by-licensed product basis or (ii) the date on which the Company has made all milestone payments pursuant to the terms of the Lilly License Agreement, unless terminated earlier by the parties. In no event will the term of the Lilly License Agreement exceed 15 years past the anniversary of the first commercial sale of a xanomeline product. The Company may terminate the Lilly License Agreement for any reason with proper prior notice to Eli Lilly. Either party may terminate the Lilly License Agreement upon an uncured material breach by the other party.

The initial upfront payment of $0.1 million was expensed when incurred in May 2012. As of December 31, 2020, no milestones have been reached, and accordingly, no milestone payments have been made.

Intellectual Property License with PureTech Health

In March 2011, the Company entered into an exclusive license agreement (the “Patent License Agreement”) with PureTech Health, pursuant to which PureTech Health granted the Company an exclusive license to patent rights relating to combinations of a muscarinic activator with a muscarinic inhibitor for the treatment of central nervous system disorders.

In connection with the Patent License Agreement, the Company has agreed to make milestone payments to PureTech Health of up to an aggregate of $10 million upon the achievement of specified development and regulatory milestones. In addition, the Company is obligated to pay PureTech Health low single-digit royalties on the worldwide net sales of any commercialized product covered by the licenses granted under the Patent License Agreement. In the event that the Company sublicenses any of the patent rights granted under the Patent License Agreement, the Company will be obligated to pay PureTech Health royalties within the range of 15% to 25% on any income we receive from the sublicensee, excluding royalties.

The Company may terminate the Patent License Agreement for any reason with proper prior notice to PureTech Health. Either party may terminate the Patent License Agreement upon an uncured material breach by the other party.

In December 2020, the Company paid $2.0 million to PureTech Health, having reached the milestone of Phase 3 clinical trial commencement. The Company incurred no expenses related to the Patent License provided by PureTech Health during the years ended December 31, 2019 and 2018. The Company had no outstanding liabilities to PureTech Health related to the Patent License at December 31, 2020 or 2019.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future but have not yet been made. To date, the Company has not paid any claims or been required to defend any action related to its indemnification obligations. However, the Company may incur charges in the future as a result of these indemnification obligations.

Contingencies

From time to time, the Company may have certain contingent liabilities that arise in the ordinary course of its business activities. The Company accrues a liability for such matters when it is probable that future expenditures will be made, and such expenditures can be reasonably estimated.

Litigation

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities as of December 31, 2020.

Note 12. Income Taxes

During the years ended December 31, 2020, 2019 and 2018, the Company recorded income tax benefit (expense) of less than $(0.1) million, $0, and $0, respectively. The Company did not recognize any significant tax expense for the years ended December 31, 2020, 2019, or 2018 as the Company was subject to a full valuation allowance.

A reconciliation of the differences between the effective tax rates of the Company and the U.S. federal statutory tax rate are as follows:

	Year Ended December 31,		
	2020	2019	2018
Statutory tax rate	21.0%	21.0%	21.0%
State taxes, net of federal benefit	10.3%	6.7%	5.0%
Share-based compensation	21.3%	0.0%	-1.0%
Change in derivative liability	0.0%	-0.1%	-0.5%
Non-deductible interest expense	0.0%	-0.4%	-3.1%
Other	-0.1%	0.3%	0.0%
Tax credits	3.2%	4.9%	3.0%
Change in valuation allowance	-55.7%	-32.4%	-24.4%
Effective Income tax rate	**0.0%**	**0.0%**	**0.0%**

Significant components of the Company's deferred tax assets and liabilities at December 31, 2020 and 2019 are as follows:

	December 31,	
	2020	2019
Deferred tax assets:		
Operating tax losses	$ 47,349	$ 14,145
Tax Credit Carryforwards	5,613	3,028
Fixed Assets	—	—
Accrued expenses	631	580
Lease liability	702	—
Share-based compensation	5,923	3,613
Deferred tax assets	60,218	21,366
Valuation allowance	(59,563)	(21,339)
Deferred tax liabilities:		
ROU assets	(633)	—
Depreciation	(22)	(27)
Deferred tax liabilities	(655)	(27)
Net Deferred Tax Asset / (Liability)	$ —	$ —

Deferred income taxes reflect the net tax effect of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amount used for income tax purposes. The Company applied the separate return method for allocation of current and deferred tax expense. As of August 1, 2018, PureTech no longer held 80% of the outstanding shares of the Company. Therefore, from that date onward, the Company was required to file a separate U.S. federal income tax return. As of July 2, 2019, PureTech no longer held 50% of the outstanding shares of the Company. As such, we have filed separate state income tax returns subsequent to this date.

At December 31, 2020, on a separate return method, the Company has federal net operating loss carryforwards totaling $179.8 million of which $9.7 million begin to expire in 2029 and $170.1 million can be carried forward indefinitely. In addition, we had state net operating loss carryforwards totaling $151.7 million which begin to expire in 2030. Lastly, the Company has federal research credits of $5.0 million and state research credits of $0.8 million which begin to expire in 2031. Because the Company had historically been a subsidiary of PureTech, $179.4 million and $131.7 million of the federal and state net operating loss carryforwards, respectively, can be used to offset income on our future tax returns. In addition, $4.9 million and $0.8 million of the federal and state tax credit carryforwards, respectively, can be used to offset tax due on our future tax returns. Our net operating loss and tax credit carryforwards could, in whole or in part, expire unused and be unavailable to offset future income tax liabilities.

Management has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets, which are comprised principally of net operating loss carryforwards and tax credit carryforwards. Under the applicable accounting standards, management has considered the Company's history of losses and concluded that it is more likely than not that the Company will not recognize the benefits of deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets at December 31, 2020. The valuation allowance increased by $38.2 million during the year ended December 31, 2020 which primarily relates to the current year operating loss and tax credits generated.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed a Section 382 study during the year ended December 31, 2020, and while certain tax attributes are subject to annual limitations, none are expected to be restricted in their future utilization if the Company earns sufficient future profits to utilize the tax attributes. Future transactions involving the issuance or transfer of the Company’s stock could result in additional ownership changes which may limit the amount of tax attributes available to offset future tax liabilities.

On March 27, 2020, the Coronavirus Aid, Relief and Economic Security (“CARES”) Act was enacted and signed into law. Among other things, the CARES Act allows for a five-year carryback of Federal net operating losses generated in tax years beginning in 2018, 2019, or 2020 and removes the 80% taxable income limitation for net operating loss deductions for tax years beginning before January 1, 2021. The Company has evaluated the income tax ramifications of the CARES Act and has determined that there is no material impact to its overall income tax position.

The Company accounts for uncertain tax positions pursuant to ASC 740 which prescribes a recognition threshold and measurement process for financial statement recognition of uncertain tax positions taken or expected to be taken in a tax return. If the tax position meets this threshold, the benefit to be recognized is measured as the tax benefit having the highest likelihood of being realized upon ultimate settlement with the taxing authority. As of December 31, 2020, the Company has not recorded any unrecognized tax benefits. The Company does not expect any material change in unrecognized tax benefits within the next twelve months. The Company’s policy is to record interest and penalties as a component of income tax expense. As of December 31, 2020, the Company has not accrued interest or penalties related to any uncertain tax positions.

We are subject to taxation in the United States federal and certain state jurisdictions. The Company has incurred operating losses since inception, and therefore, the losses in all periods may be adjusted by taxing jurisdictions in future periods in which they are utilized.

Note 13. Related Party Transactions

PureTech Health Management Consulting Services and Overhead Agreement

The Company previously engaged PureTech Health, a related party, to provide, among other things, management expertise, strategic advice, administrative support, computer and telecommunications services and office infrastructure. In exchange for providing such services, the Company paid PureTech Health a monthly fee. In addition, PureTech Health periodically invoiced the Company for out-of-pocket expenses reasonably incurred in connection with providing such business services.

The Company incurred general and administrative costs for management services provided by PureTech Health totaling less than $0.1 million and $0.2 million in the years ended December 31, 2019 and 2018, respectively. The Company had outstanding current liabilities to PureTech Health of less than $0.1 million at December 31, 2019, which were recorded as accounts payable in the consolidated balance sheets. As of and for the year ended December 31, 2020, the Company had no outstanding liabilities to PureTech Health and no general and administrative costs for management services were incurred.

Note 14. 401(k) Savings Plan

The Company has a 401(k) retirement plan in which substantially all U.S. employees are eligible to participate. Eligible employees may elect to contribute up to the maximum limits, as set by the Internal Revenue Service, of their eligible compensation. The total contribution expense for the Company was $0.2 million for the year ended December 31, 2020 and less than $0.1 million for each of the years ended December 31, 2019 and 2018.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

We maintain “disclosure controls and procedures” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating our 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 their objectives, and management necessarily applies its judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, who serve as our principal executive officer and principal financial and accounting officer, respectively, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2020.

Internal Control Over Financial Reporting

Management’s Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, a company’s principal executive officer and principal financial officer, or persons performing similar functions, and effected by a company’s board of directors, management, and other personnel, 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 and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of a company’s assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that a company’s receipts and expenditures are being made only in accordance with authorizations of the company’s management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

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

Under the supervision of and with the participation of our principal executive officer and principal financial officer, our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2020 based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control—Integrated Framework (2013 framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2020.

Our independent registered public accounting firm has issued an attestation report of our internal control over financial reporting, which is included in Item 8, “Consolidated Financial Statements and Supplementary Data” appearing elsewhere in this Annual Report on Form 10-K.

Changes in Internal Control Over Financial Reporting

There have been no changes in internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the fiscal quarter ended December 31, 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

1. Consolidated Financial Statements

The following documents are included in this Annual Report on Form 10-K:

Report of Independent Registered Public Accounting Firm
Consolidated Financial Statements
- Consolidated Balance Sheets
- Consolidated Statements of Operations
- Consolidated Statements of Comprehensive Loss
- Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
- Consolidated Statements of Cash Flows
- Notes to Consolidated Financial Statements

2. Financial Statement Schedules

Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

3. Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Amended and Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on July 3, 2019, and incorporated by reference herein)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed with the SEC on July 3, 2019, and incorporated by reference herein)
4.1	Specimen stock certificate evidencing the shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, filed with the SEC on June 17, 2019, and incorporated by reference herein)
4.2	Amended and Restated Investors' Rights Agreement, dated as of March 15, 2019, among the Registrant and the other parties thereto (filed as Exhibit 4.2 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
4.3	Description of Capital Stock (filed as Exhibit 4.3 to the Registrant's Annual Report on Form 10-K, filed with the SEC on March 24, 2020, and incorporated by reference herein)
10.1#	2009 Stock Incentive Plan, as amended, and forms of award agreements thereunder (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.2#	2019 Stock Option and Incentive Plan (filed as Exhibit 10.2 to the Registrant's Registration Statement on Form S-1, filed with the SEC on June 17, 2019, and incorporated by reference herein)
10.3#	Form of Incentive Stock Option Agreement under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.4#	Form of Non-Qualified Stock Option Agreement for Company Employees under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.4 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.5#	Form of Non-Qualified Stock Option Agreement for Non-Employee Directors under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.6#	Form of Restricted Stock Award Agreement under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.6 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.7#	Form of Restricted Stock Unit Award Agreement for Company Employees under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.8#	Form of Restricted Stock Unit Award Agreement for Non-Employee Directors under the Registrant's 2019 Stock Option and Incentive Plan (filed as Exhibit 10.8 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.9#	2019 Employee Stock Purchase Plan (filed as Exhibit 10.9 to the Registrant's Registration Statement on Form S-1, filed with the SEC on June 17, 2019, and incorporated by reference herein)
10.10+	License Agreement, dated as of May 9, 2012, by and between the Registrant and Eli Lilly and Company (filed as Exhibit 10.10 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.11+	Exclusive Patent License Agreement, dated as of March 4, 2011, as amended on February 1, 2013 and February 25, 2015, by and between the Registrant and PureTech Health LLC (filed as Exhibit 10.11 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.12	Office Lease, dated as of November 2, 2018, by and between the Registrant and T-C 33 Arch Street LLC (filed as Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)

Exhibit Number	Description of Exhibit
10.13	Amendment to Office Lease, dated as of January 22, 2020, by and between the Registrant and T-C 33 Arch Street LLC (filed as Exhibit 10.13 to the Registrant's Annual Report on Form 10-K, filed with the SEC on March 24, 2020, and incorporated by reference herein)
10.14	Business Services, Personnel and Information Management Agreement, dated as of July 24, 2009, by and among the Registrant, PureTech Management, Inc., PureTech Health LLC and PureTech Health plc (filed as Exhibit 10.13 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.15#	Employment Agreement, between the Registrant and Steven Paul (filed as Exhibit 10.14 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.16#	Employment Agreement, between the Registrant and Andrew Miller (filed as Exhibit 10.15 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.17#	Employment Agreement, between the Registrant and Stephen Brannan (filed as Exhibit 10.16 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.18#	Amended and Restated Employment Agreement, dated July 3, 2019, by and between Karuna Therapeutics, Inc. and Troy Ignelzi (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed with the SEC on November 7, 2019, and incorporated by reference herein)
10.19#	Form of Director Indemnification Agreement (filed as Exhibit 10.17 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.20#	Form of Officer Indemnification Agreement (filed as Exhibit 10.18 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
10.21#	Senior Executive Cash Incentive Bonus Plan (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1, filed with the SEC on May 31, 2019, and incorporated by reference herein)
21.1	List of Subsidiaries of the Registrant (filed as Exhibit 21.1 to the Registrant's Annual Report on Form 10-K filed on March 24, 2020)
23.1*	Consent of KPMG LLP, independent registered public accounting firm
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.
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.
32.1**	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Schema Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

* Filed herewith

** Furnished herewith

\+ Certain portions of this exhibit have been omitted because they are not material and would likely cause competitive harm to the registrant if disclosed.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

SIGNATURES

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

KARUNA THERAPEUTICS, INC.

Date: February 25, 2021

By: /s/ Steven Paul, M.D.
Steven Paul, M.D.
Chief Executive Officer. President and Chairman
(Principal Executive Officer)

Date: February 25, 2021

By: /s/ Troy Ignelzi
Troy Ignelzi
Chief Financial Officer
(Principal Financial and Accounting Officer)

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

Signature	Title	Date
/s/ Steven Paul, M.D. Steven Paul, M.D.	Chief Executive Officer, President and Chairman (Principal Executive Officer)	February 25, 2021
/s/ Troy Ignelzi Troy Ignelzi	Chief Financial Officer (Principal Financial and Accounting Officer)	February 25, 2021
/s/ Christopher J. Coughlin Christopher J. Coughlin	Director	February 25, 2021
/s/ James Healy, M.D., Ph.D. James Healy, M.D., Ph.D.	Director	February 25, 2021
/s/ Jeffrey Jonas, M.D. Jeffrey Jonas, M.D.	Director	February 25, 2021
/s/ Robert Nelsen Robert Nelsen	Director	February 25, 2021
/s/ Laurie Olson Laurie Olson	Director	February 25, 2021
/s/ Atul Pande, M.D. Atul Pande, M.D.	Director	February 25, 2021
/s/ Heather Preston, M.D. Heather Preston, M.D.	Director	February 25, 2021
/s/ Denice Torres Denice Torres	Director	February 25, 2021
/s/ David E. Wheadon, M.D. David E. Wheadon, M.D.	Director	February 25, 2021

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors
Karuna Therapeutics, Inc.:

We consent to the incorporation by reference in the registration statements (No. 333-239657) on Form S-3 and (No. 333-232521 and No. 333-237360) on Form S-8 of Karuna Therapeutics, Inc. of our report dated February 25, 2021, with respect to the consolidated balance sheets of Karuna Therapeutics, Inc. and subsidiary as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the years in the three-year period ended December 31, 2020, and the related notes, and the effectiveness of internal control over financial reporting as of December 31, 2020, which report appears in the December 31, 2020 annual report on Form 10-K of Karuna Therapeutics, Inc.

/s/ KPMG LLP

Boston, Massachusetts
February 25, 2021

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO RULE 13A-14(A) / RULE 15D-14(A) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Steven Paul, M.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Karuna Therapeutics, 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 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 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: February 25, 2021

/s/ Steven Paul

Steven Paul, M.D.
Chief Executive Officer, President and Chairman
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO RULE 13A-14(A) / RULE 15D-14(A) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Troy Ignelzi, certify that:

1. I have reviewed this Annual Report on Form 10-K of Karuna Therapeutics, 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 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 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: February 25, 2021

/s/ Troy Ignelzi

Troy Ignelzi
Chief Financial Officer
(Principal Financial and Accounting Officer)

CERTIFICATIONS OF PRINCIPAL EXECUTIVE OFFICER AND PRINCIPAL FINANCIAL OFFICER PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with this Annual Report on Form 10-K of Karuna Therapeutics, Inc. (the "Company") for the fiscal year ended December 31, 2020 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his or her knowledge:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: February 25, 2021

/s/ Steven Paul
Steven Paul, M.D.
Chief Executive Officer, President and Chairman
(Principal Executive Officer)

/s/ Troy Ignelzi
Troy Ignelzi
Chief Financial Officer
(Principal Financial and Accounting Officer)