KARUNA
THERAPEUTICS™

2022 Annual Report

Dear Shareholders,

A significant and growing number of people are struggling with mental illness. It is estimated that 1 in 5 people in the United States are living with a mental health condition, and we at Karuna have an opportunity to help them by discovering and developing new and differentiated treatments for a broad range of conditions, including schizophrenia and psychosis in Alzheimer's disease. Karuna means *"action taken to diminish the suffering of others."* Karuna is not only a name, but it is the core of who we are and what we do. We are building a leading neuroscience company defined by innovative science, strong R&D and commercial capabilities, and great people and culture.

2022 was a strong year for the company. We reported positive data from our registrational EMERGENT-2 trial of KarXT in schizophrenia, which confirmed the findings from prior studies and provided a clear pathway for an NDA submission. Earlier this year, those findings were replicated once again with positive data from our registrational EMERGENT-3 trial. KarXT has now demonstrated statistically significant and clinically meaningful reductions in schizophrenia symptoms, and was generally well-tolerated, in three consecutive registration quality studies. We also completed enrollment in EMERGENT-4, and made excellent progress with EMERGENT-5, both of which are designed to provide the required long-term safety data for our NDA submission in 2023. Beyond the EMERGENT program, we are studying KarXT in two additional indications—adjunctive treatment of schizophrenia and psychosis in Alzheimer's disease, or AD, which could significantly expand the clinical utility and commercial potential of KarXT.

We focused on growing our pipeline. Our discovery and business development groups concentrate on addressing the substantial need for new and better treatments in psychiatry and neurology with novel mechanisms and validated targets. We are disciplined in terms of where and how much we invest. Our licensing of investigational TRPC4/5 inhibitors for mood and anxiety disorders this year is an example of the types of transactions that make sense for Karuna. It met all our criteria strategically, scientifically, and financially.

We strengthened our organizational capabilities. We doubled our workforce and now have more than 240 employees across our discovery, development, medical affairs, commercial, and G&A functions, all of whom are committed to and focused on supporting the discovery, development, and potential commercialization of new compounds for conditions such as schizophrenia, AD psychosis, depression, and anxiety, among other conditions.

Our successes are a testament to our employees. They include the clinical researchers who conduct our trials, the regulatory professionals who prepare our submissions, the manufacturing specialists who make our product candidates, the finance executives who manage our budgets, and our administrative personnel who keep the trains on time, among many others. They are the people who make it happen every day and are motivated by the patients we are here to serve and by the goal of building a great company.

We are transitioning to a fully integrated R&D and commercial organization. We are focused on submitting our NDA and the pre-commercialization activities for KarXT. The company is well capitalized and has the management team needed to scale the business.

I would like to thank our employees, partners, and shareholders for their collective commitment and support.

Sincerely,

Bill Meury
President and Chief Executive Officer

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, 2022

OR

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

For the transition period from _____to

Commission file number 001-38958

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)**
99 High Street, 26th Floor 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. ☒

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

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

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

As of June 30, 2022, 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 that date, was $2,920.6 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, 2023, there were 34,515,033 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 2023 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, 2022, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Karuna Therapeutics, Inc.
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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, KAR-2618 (formerly GFB-887) 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;
- the ability and efforts of our licensee, Zai Lab (Shanghai) Co., Ltd. (Zai), to successfully develop and commercialize KarXT, if approved, in mainland China, Hong Kong, Macau, and Taiwan, also referred to as Greater China, under the terms and conditions of our license agreement;
- our plans to enter into collaborations for the development and commercialization of product candidates and the potential benefits of any such 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

Our business is subject to numerous risks and uncertainties that you should be aware of before making an investment decision, including those highlighted in "Item 1A. Risk Factors" in this Annual Report on Form 10-K. These risks include, but are not limited to, the following:

- 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.
- 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.
- Our operations in foreign jurisdictions, and those of our collaborators, may be impacted by economic, political and social conditions in such jurisdictions, as well as government policies, any of which could impact our ability to operate in such jurisdictions.
- The results to date of our preclinical studies and clinical trials do not guarantee that we will succeed in developing KarXT or any other product candidate into a marketable product. Initial data in our clinical trials may not be predictive of results obtained when these trials are completed or in subsequent trials.
- We currently have limited 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.
- 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 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 a clinical-stage biopharmaceutical company driven to create and deliver transformative medicines for people living with psychiatric and neurological conditions. Our pipeline is primarily built on the broad therapeutic potential of our proprietary lead product candidate, KarXT (xanomeline-trospium), an oral modulator of muscarinic receptors that are located both in the central nervous system, or CNS, and various peripheral tissues. KarXT combines xanomeline, a novel muscarinic agonist, with trospium, an approved muscarinic antagonist, to preferentially stimulate muscarinic receptors in the CNS. We are initially developing KarXT for the treatment of acute psychosis in adults with schizophrenia, as well as for the treatment of psychosis in Alzheimer's disease, or AD.

Schizophrenia is a chronic disabling disorder that is characterized by recurring episodes of psychosis requiring long-term treatment with antipsychotic drugs in most patients. Psychotic symptoms, also known as positive symptoms, include hallucinations and delusions. As a result of the disease, patients with schizophrenia also experience negative symptoms, such as apathy, reduced social drive, loss of motivation and lack of social interest, as well as cognitive impairment. It is estimated that more than 21 million people are living with schizophrenia worldwide, with approximately 2.7 million in the United States, or approximately 0.5% to 1.0% of the United States population.

AD, an irreversible, progressive neurodegenerative brain disorder that slowly destroys memory and cognition, is the most common form of dementia, accounting for an estimated 60% to 80% of the approximately 8.4 million people living with dementia in the United States. Up to 50% of AD patients exhibit psychiatric symptoms, which often leads to institutional care in a hospital or nursing home. Although the U.S. Food and Drug Administration, or FDA, has not to date approved any drug to treat the psychotic or behavioral symptoms of AD, physicians often resort to off-label use of antipsychotic medications to treat these patients as symptoms progress and become more severe.

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.

We are initially developing KarXT for the treatment of acute psychosis in adults with schizophrenia, as well as for the treatment of psychosis in AD. 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. To our knowledge, xanomeline is the only muscarinic orthosteric agonist that has demonstrated therapeutic benefit in clinical trials in both schizophrenia and AD. Like all muscarinic orthosteric 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 the combination of xanomeline and trospium in KarXT 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.

The EMERGENT program is our clinical program evaluating KarXT for the treatment of schizophrenia as a monotherapy, and includes our completed positive Phase 2 EMERGENT-1 and Phase 3 EMERGENT-2 trials and three additional Phase 3 trials (EMERGENT-3, EMERGENT-4, and EMERGENT-5). In August 2022, we announced positive topline results from our Phase 3 EMERGENT-2 trial evaluating the efficacy, safety and tolerability of KarXT compared to placebo for the treatment of acute psychosis in adults with schizophrenia. KarXT met the primary endpoint, demonstrating a statistically significant and clinically meaningful 9.6-point reduction in Positive and Negative Syndrome Scale, or PANSS, total score compared to placebo at Week 5 (Cohen's d effect size of 0.61). KarXT also demonstrated an early and sustained statistically significant reduction of symptoms, as assessed by PANSS total score, starting at Week 2 and maintained such reduction through all timepoints in the trial. KarXT also met all secondary endpoints, demonstrating a statistically significant 2.9-point reduction in the PANSS positive symptoms subscale, a 1.8-point reduction in PANSS negative symptoms subscale, a 2.2-point reduction in PANSS negative Marder factor subscale, and a 0.6-point reduction in CGI-S score, compared to placebo at Week 5. Additionally, a statistically significant greater proportion of patients in the KarXT arm had a ≥30% reduction in PANSS total score compared with placebo at Week 5 ($p<0.0001$). KarXT was generally well-tolerated in the EMERGENT-2 trial and was not associated with common problematic side effects of current treatments, including sedation (somnolence), weight gain, and extrapyramidal symptoms. We plan to share results from exploratory endpoints in the future.

Following the positive results of EMERGENT-1 in November 2019, we had an End-of-Phase 2 meeting with the FDA, in which the FDA indicated that our completed Phase 2 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, submission in schizophrenia. As a result of our completed Phase 3 EMERGENT-2 trial, we plan to submit our NDA for KarXT for the treatment of schizophrenia to the FDA in mid-2023. We define mid-year as the second and third quarters of a calendar year. If approved, we are targeting a potential commercial launch of KarXT for the treatment of schizophrenia in the second half of 2024.

In addition to our completed Phase 2 EMERGENT-1 and Phase 3 EMERGENT-2 trials, our EMERGENT program includes the following Phase 3 trials:

- EMERGENT-3: A five-week inpatient trial evaluating the efficacy and safety of KarXT compared to placebo in 256 adults with schizophrenia in the United States and Ukraine. Enrollment for this trial completed in the fourth quarter of 2022 and we anticipate topline data in the first quarter of 2023.
- EMERGENT-4: 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. Enrollment for this trial completed in the fourth quarter of 2022.

- EMERGENT-5: A 52-week outpatient, open-label trial conducted in the United States and Puerto Rico evaluating the long-term safety and tolerability of KarXT in adults with schizophrenia who were not enrolled in EMERGENT-2 or EMERGENT-3. Enrollment for this trial began in the second quarter of 2021.

Given the unique mechanism of action of KarXT in comparison to existing standard of care therapies, we believe there is the potential for therapeutic benefit as both a monotherapy and as an adjunctive therapy for the treatment of schizophrenia. In November 2021, we initiated our Phase 3 ARISE trial evaluating the safety and efficacy of KarXT compared to placebo as an adjunctive treatment in adults with schizophrenia who have an inadequate response to their current antipsychotic therapy. This six-week, 1:1 randomized, double-blind, placebo-controlled Phase 3 outpatient trial is designed to enroll approximately 400 adults with schizophrenia who have not achieved an adequate response to their current atypical antipsychotic treatment. The primary outcome measure of the trial is change in PANSS total score of KarXT compared to placebo at week 6. Upon completion of the trial at week 6, participants have the opportunity to enroll in our ARISE-2 trial, an ongoing 52-week outpatient, open-label extension trial evaluating the long-term safety and tolerability of KarXT when dosed with atypical antipsychotic treatment. We anticipate topline data from the ARISE trial in the first half of 2024.

We plan to utilize the data from the EMERGENT and ARISE clinical programs to help inform future potential development plans for KarXT in negative and cognitive symptoms of schizophrenia, for which there are currently no approved treatments.

We are also developing KarXT as a potential treatment for psychosis related to AD. The ADEPT program, which is the clinical program evaluating KarXT as a potential treatment for psychosis related to AD, consists of the following ongoing and planned Phase 3 trials:

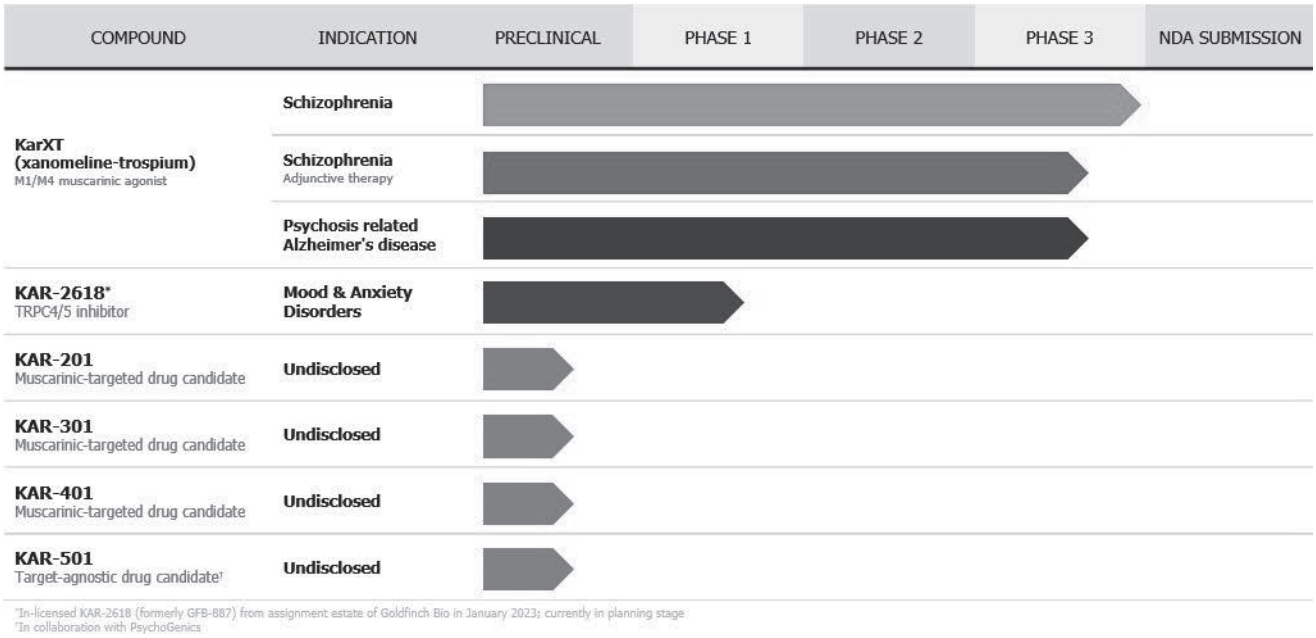
- ADEPT-1: A trial evaluating the efficacy and safety of KarXT compared to placebo in up to 400 adults with moderate to severe psychosis related to AD. This trial consists of a 12-week, single-blind treatment period, followed by a 26-week, double-blind, randomized withdrawal period in which subjects who meet the response criteria will be randomized to receive KarXT or placebo. The single-blind treatment period is designed to enroll approximately 400 adults with AD, between 55 and 90 years old, with moderate to severe hallucinations or delusions, who are living at home or at an assisted living facility. The primary objective of this trial is to evaluate relapse prevention as measured by time from randomization to relapse during the 26-week, double-blind period. Enrollment for this trial began in the third quarter of 2022 and topline data is anticipated in 2025.
- ADEPT-2: A 12-week, flexible-dose, double-blind, placebo-controlled trial evaluating the efficacy and safety of KarXT versus placebo. ADEPT-2 is expected to initiate in the second half of 2023, with topline data anticipated in 2025.
- ADEPT-3: A 52-week open-label extension trial evaluating the long-term safety and tolerability of KarXT in adults with psychosis related to AD who completed ADEPT-1 or ADEPT-2. Enrollment for this trial is anticipated to commence in 2023.

In January 2023, we entered into an exclusive global license agreement for Goldfinch Bio, Inc.'s, or Goldfinch Bio's, investigational transient receptor potential canonical 4 and 5 (TRPC4/5) channel candidates, including the lead clinical-stage TRPC4/5 candidate, KAR-2618 (formerly GFB-887), after confirming select properties of KAR-2618 under a material transfer agreement. KAR-2618 has been dosed in over 100 humans across Goldfinch Bio’s clinical trials. We intend to develop KAR-2618 for the treatment of mood and anxiety disorders, and plan to provide details regarding the expected development of KAR-2618 in the second half of 2023.

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 psychosis related to AD, including the role of muscarinic receptors in the 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, and, subject to FDA approval, transition to a fully integrated R&D and commercial organization.

Pipeline

We are advancing a pipeline of therapeutic programs with KarXT to address psychiatric conditions, such as schizophrenia and psychosis related to AD. 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. In addition, we intend to develop our recently acquired lead investigational TRPC4/5 candidate, KAR-2618, for the treatment of mood and anxiety disorders, and plan to provide details regarding the expected development of KAR-2618 in the second half of 2023.



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.

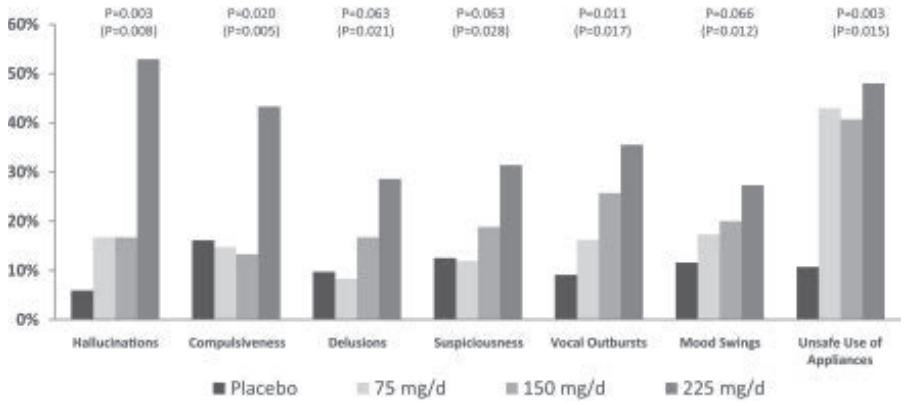
Xanomeline Background

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, support 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

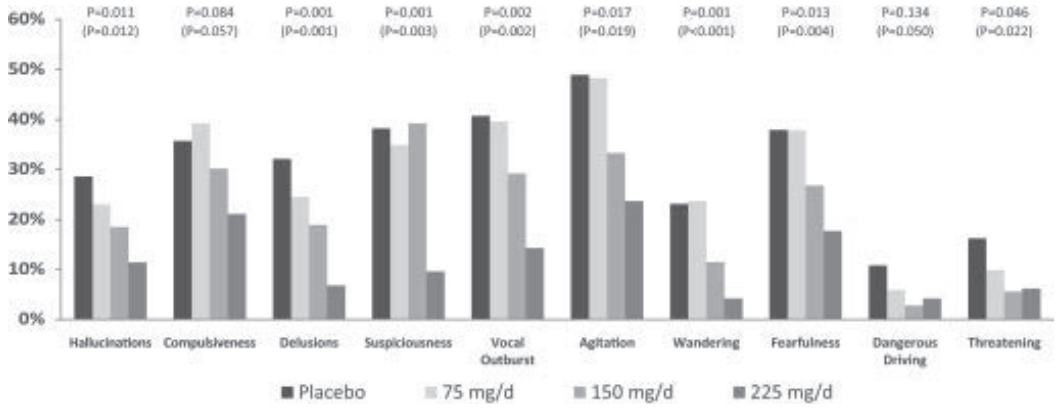
Eli Lilly and Company, or Eli Lilly, conducted a 343-patient, randomized, double-blind, placebo-controlled Phase 2 clinical trial of xanomeline in patients with mild to moderate AD, administering up to 225 mg of xanomeline daily (75 mg three times a day, or TID), for 24 weeks. In this clinical trial, 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



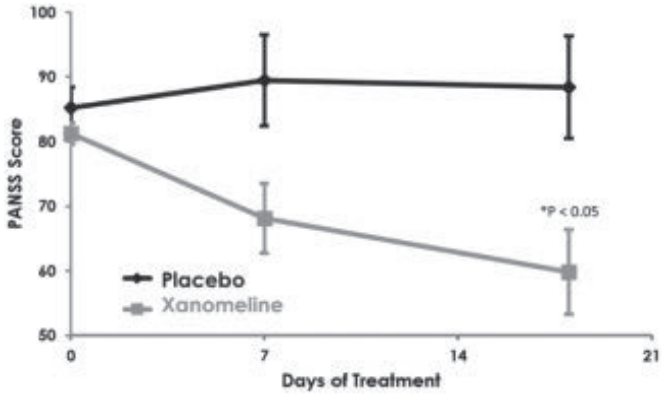
p-value represents the comparison of the 225 mg xanomeline arm compared to placebo and, in the case of the p-value in parenthesis, the dose-response analysis.

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.

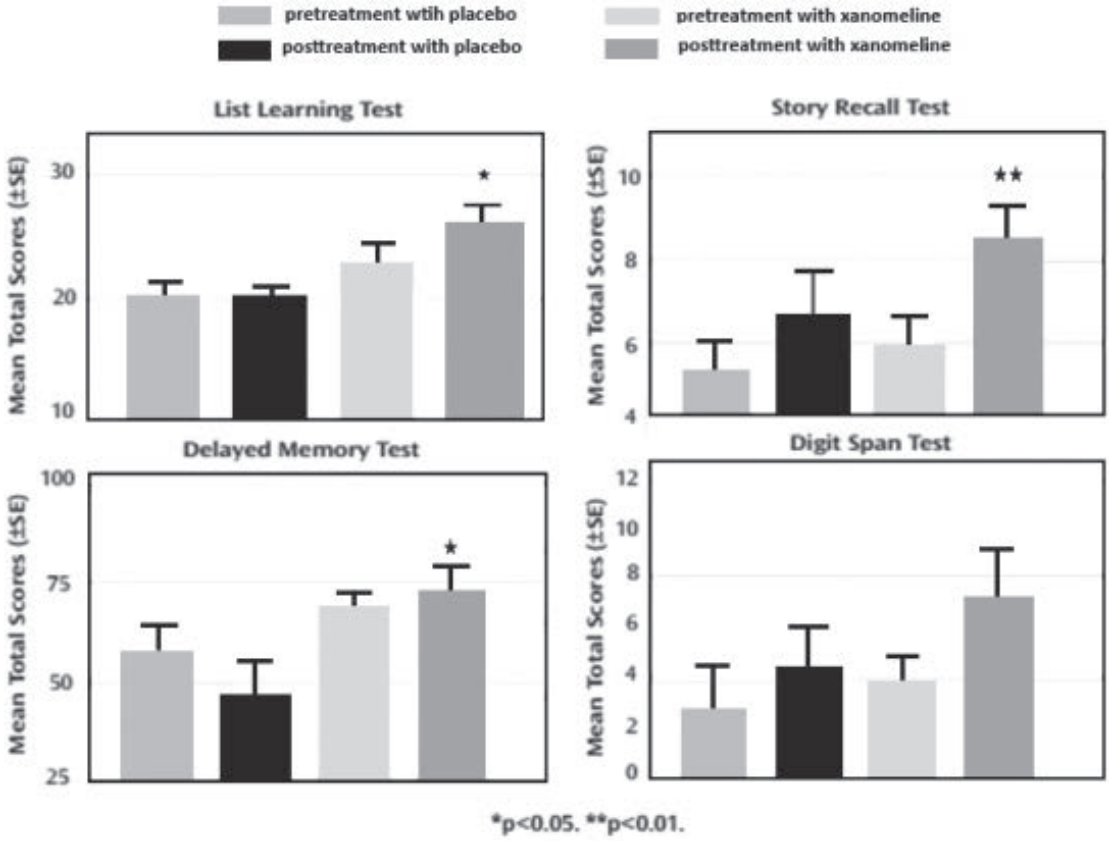
Xanomeline for the Treatment of Psychotic Symptoms in Schizophrenia

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

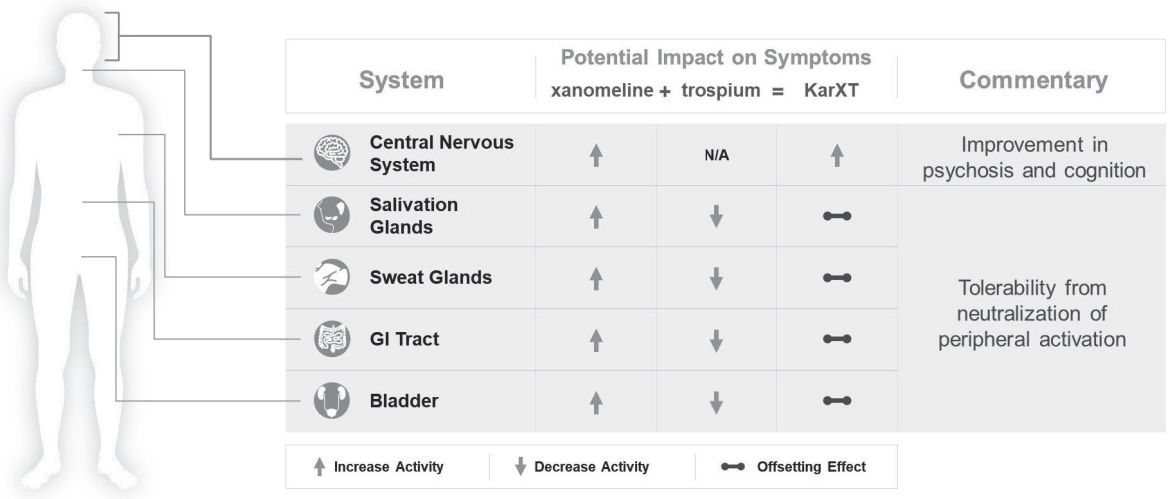


Limitations of Xanomeline

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 initially selected xanomeline based on the results of the two third-party, randomized, double-blind, placebo-controlled clinical trials, as well as the results of a wide variety of preclinical studies conducted by third parties, which supported 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, Phase 2 and Phase 3 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 clinically 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, or TEAEs, 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 to date). 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 twice daily, or 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, or IND, application to the FDA for KarXT for the treatment of schizophrenia which went into effect in August 2016.

KarXT for the Treatment of Psychosis in Patients with Schizophrenia as a Monotherapy

Schizophrenia is a chronic, severe and disabling brain 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. In 2017, an estimated 2.7 million people living in the United States, 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 20-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 many neuropsychiatric disorders, including 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 $12 billion in 2020 and are expected to exceed $26 billion by 2030, 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 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 dementia-related psychosis, or 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.

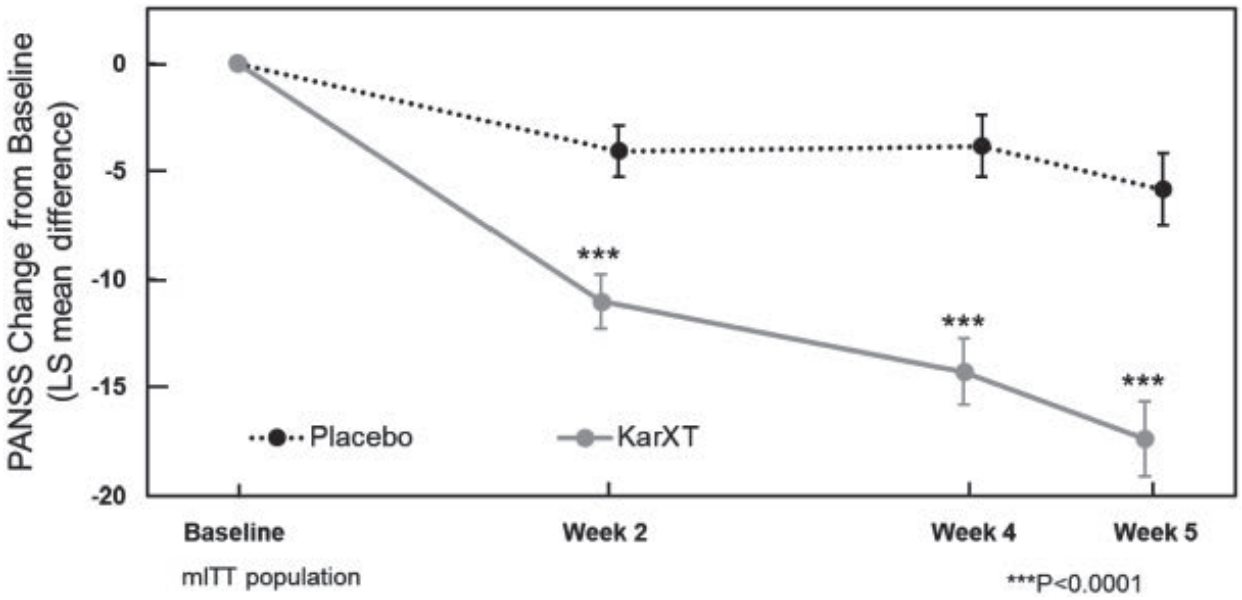
Our Completed EMERGENT-1 Phase 2 Clinical Trial for the Treatment of Acute Psychosis in Adults with Schizophrenia

In September 2018, we initiated EMERGENT-1, a multi-site, double-blind, placebo-controlled, five-week, inpatient Phase 2 clinical trial of KarXT in adults 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 negative Marder Factor subscale, a cognitive battery and the clinical global impression (CGI-S).

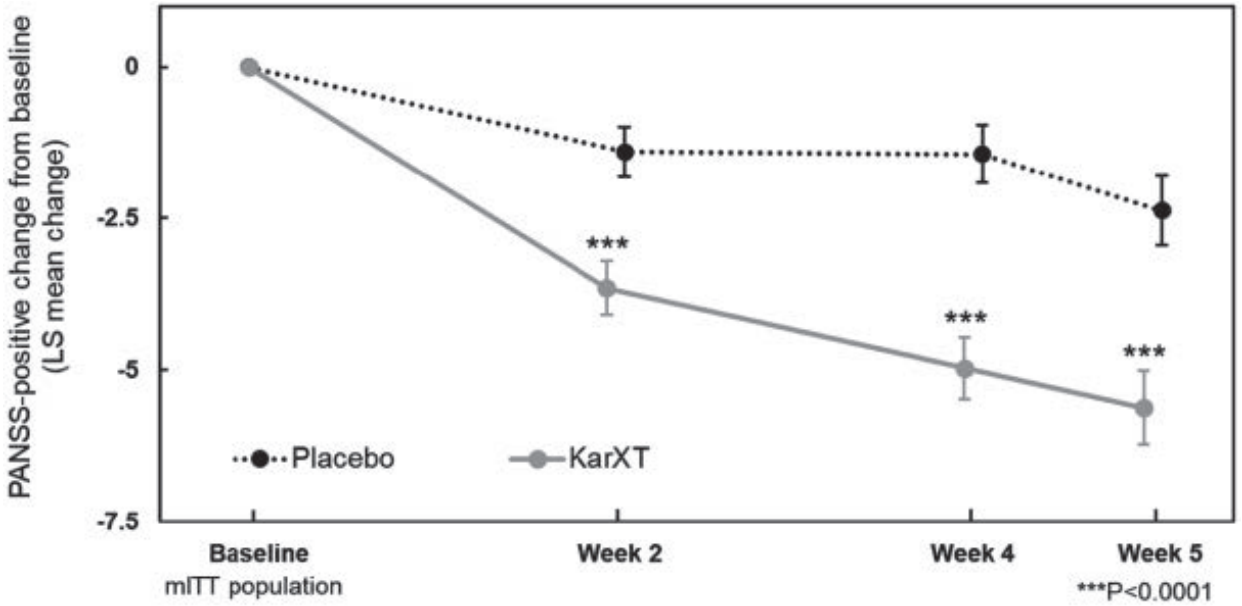
In November 2019, we announced topline results from our EMERGENT-1 trial, in which KarXT met the trial's primary endpoint with a statistically significant ($p<0.0001$) and clinically meaningful 11.6 point mean reduction in PANSS total score over placebo (-17.4 KarXT vs. -5.9 placebo) at week 5 (Cohen's d effect size of 0.75). 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 PANSS total score, PANSS-positive subscale, and the PANSS-negative subscale had statistically significant separation at every assessment throughout the trial.

We also analyzed additional pre-specified secondary endpoints, including PANSS negative Marder factor subscale, 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 negative Marder factor subscale (-3.9 KarXT v. -1.3 placebo) at week five ($p<0.001$). The PANSS negative Marder factor subscale 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 ($p=0.151$).

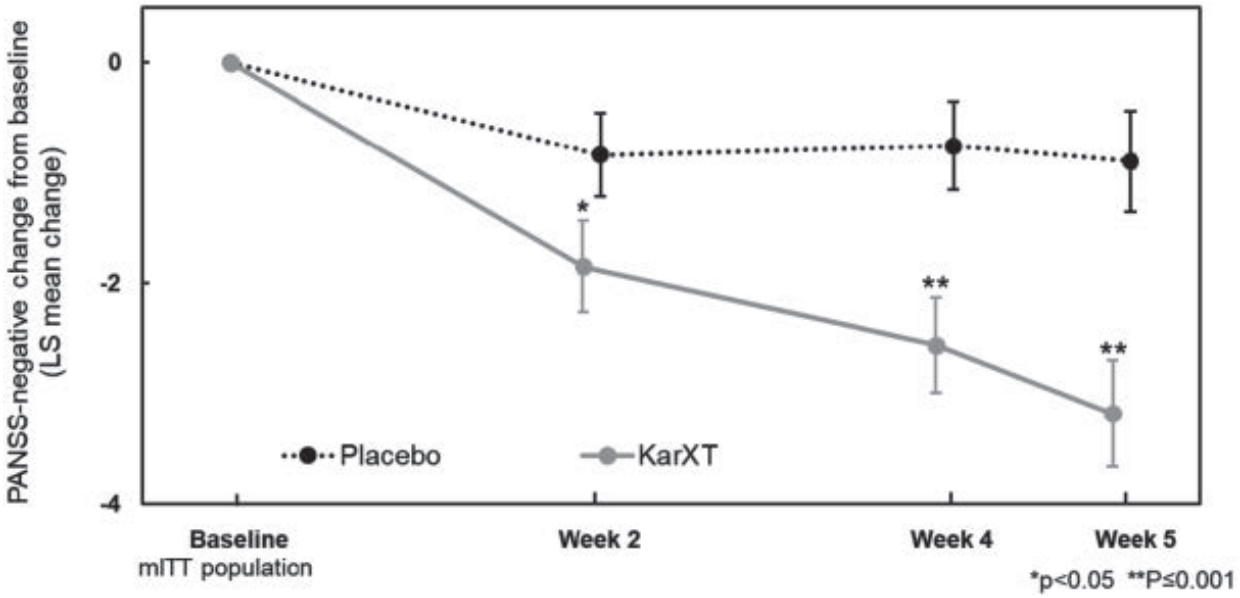
Effect of KarXT on PANSS Total Score (EMERGENT-1)



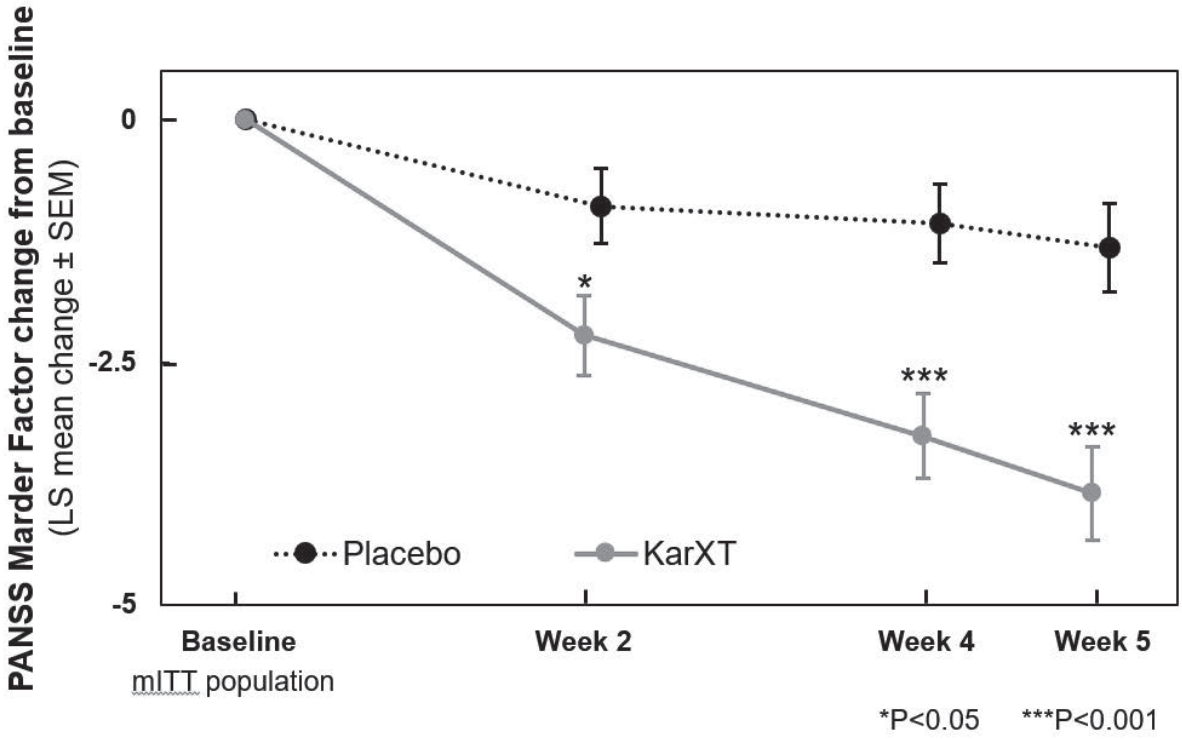
Effect of KarXT on PANSS-positive subscale (EMERGENT-1)



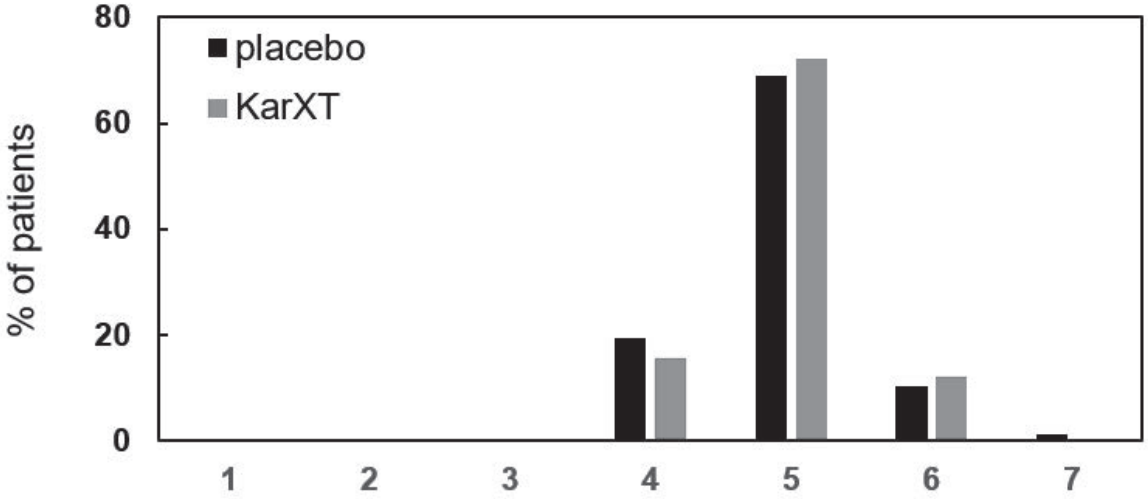
Effect of KarXT on PANSS-negative subscale (EMERGENT-1)



Effect of KarXT on PANSS negative Marder factor subscale (EMERGENT-1)

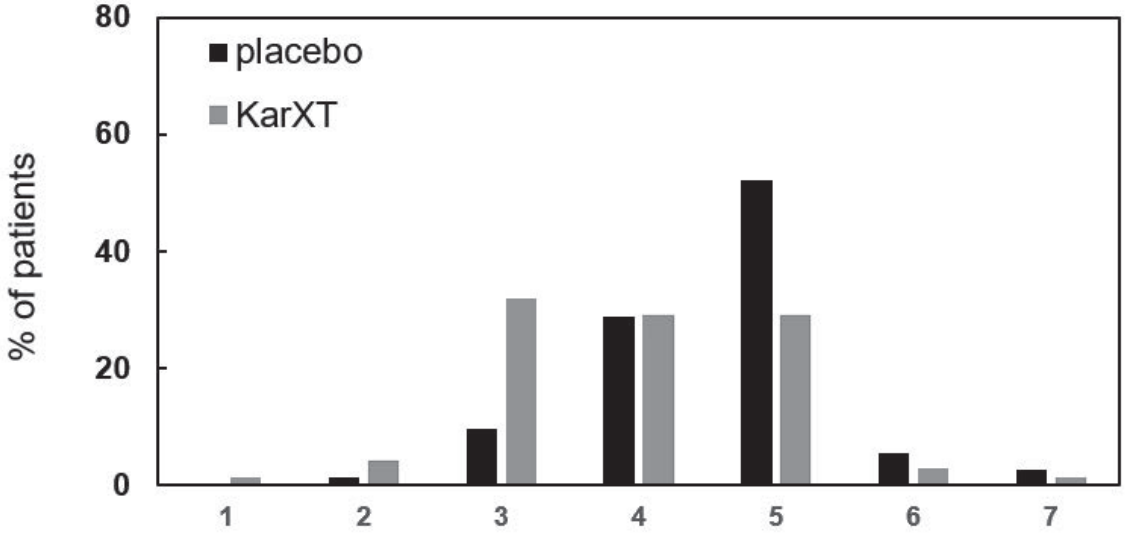


CGI-S distribution at baseline (EMERGENT-1)



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 (EMERGENT-1)



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

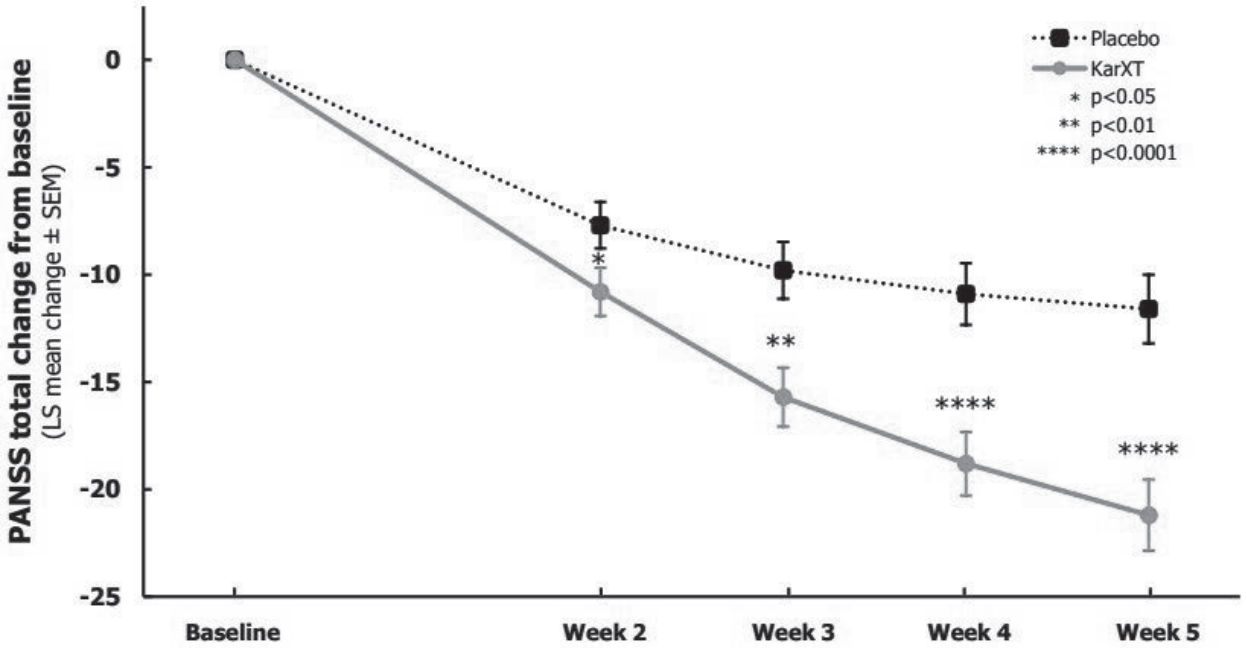
KarXT was observed to be well tolerated in the Phase 2 EMERGENT-1 trial. The overall discontinuation rate in the KarXT treatment arm was similar to placebo (20% on KarXT vs. 21% on placebo) and the number of discontinuations due to TEAEs was equal in the two arms (n=2 on KarXT and n=2 on placebo). No 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 TEAE 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, dyspepsia, 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 TEAEs were mild or moderate.

Our Completed Phase 3 EMERGENT-2 Clinical Trial for the Treatment of Acute Psychosis in Adults with Schizophrenia

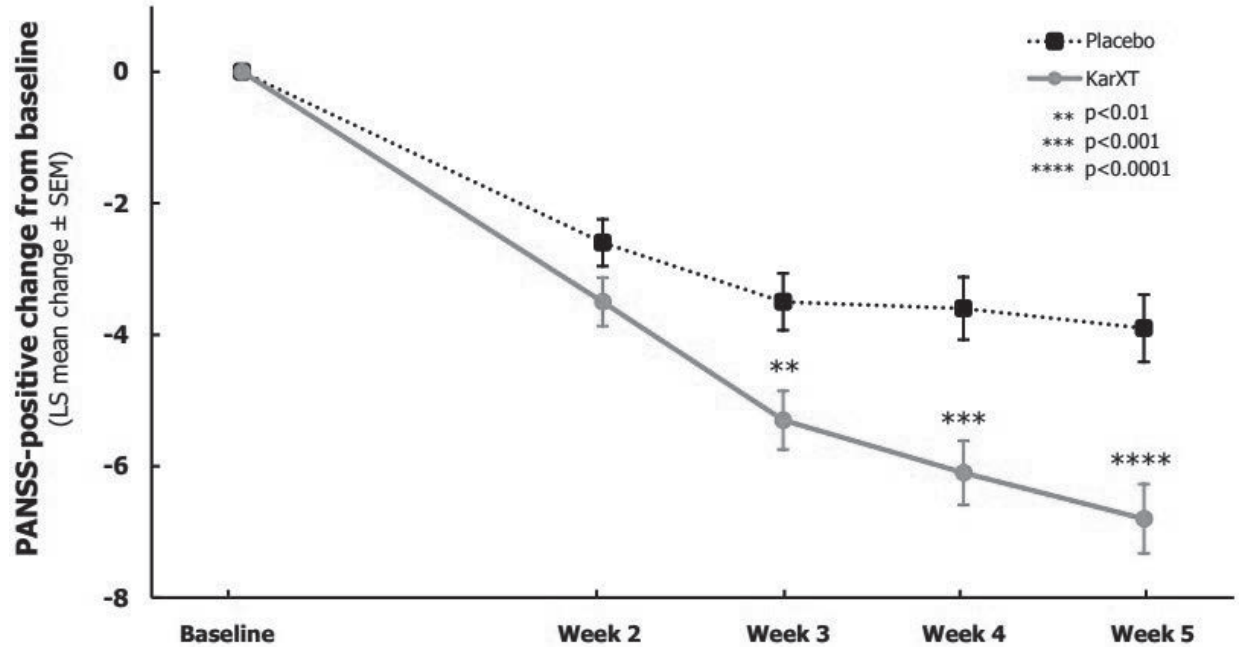
In December 2020, we initiated EMERGENT-2, a multi-site, double-blind, five-week, inpatient Phase 3 clinical trial evaluating the efficacy, safety and tolerability of KarXT compared to placebo for the treatment of acute psychosis in adults with schizophrenia. We enrolled 246 patients in this trial and 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 and secondary endpoints as our Phase 2 EMERGENT-1 clinical trial.

In August 2022, we announced positive topline results from EMERGENT-2 trial, in which KarXT met the primary endpoint, demonstrating a statistically significant and clinically meaningful 9.6-point reduction in PANSS total score compared to placebo (-21.2 KarXT vs. -11.6 placebo, $p<0.0001$) at Week 5 (Cohen’s d effect size of 0.61). KarXT also demonstrated an early and sustained statistically significant reduction of symptoms, as assessed by PANSS total score, starting at Week 2 and maintained such reduction through all timepoints in the trial. KarXT also met all secondary endpoints, demonstrating a statistically significant 2.9-point reduction in the PANSS positive symptoms subscale (-6.8 KarXT vs. -3.9 placebo, $p<0.0001$), a 1.8-point reduction in PANSS negative symptoms subscale (-3.4 KarXT vs. -1.6 placebo, $p=0.0055$), a 2.2-point reduction in PANSS negative Marder factor subscale (-4.2 KarXT vs. -2.0 placebo, $p=0.022$), and a 0.6-point reduction in CGI-S score (-1.2 KarXT vs. -0.7 placebo, $p<0.0001$), compared to placebo at Week 5. Additionally, a statistically significant greater proportion of patients in the KarXT arm had a ≥30% reduction in PANSS total score compared to placebo at Week 5 ($p<0.0001$). We plan to share results from exploratory endpoints in the future.

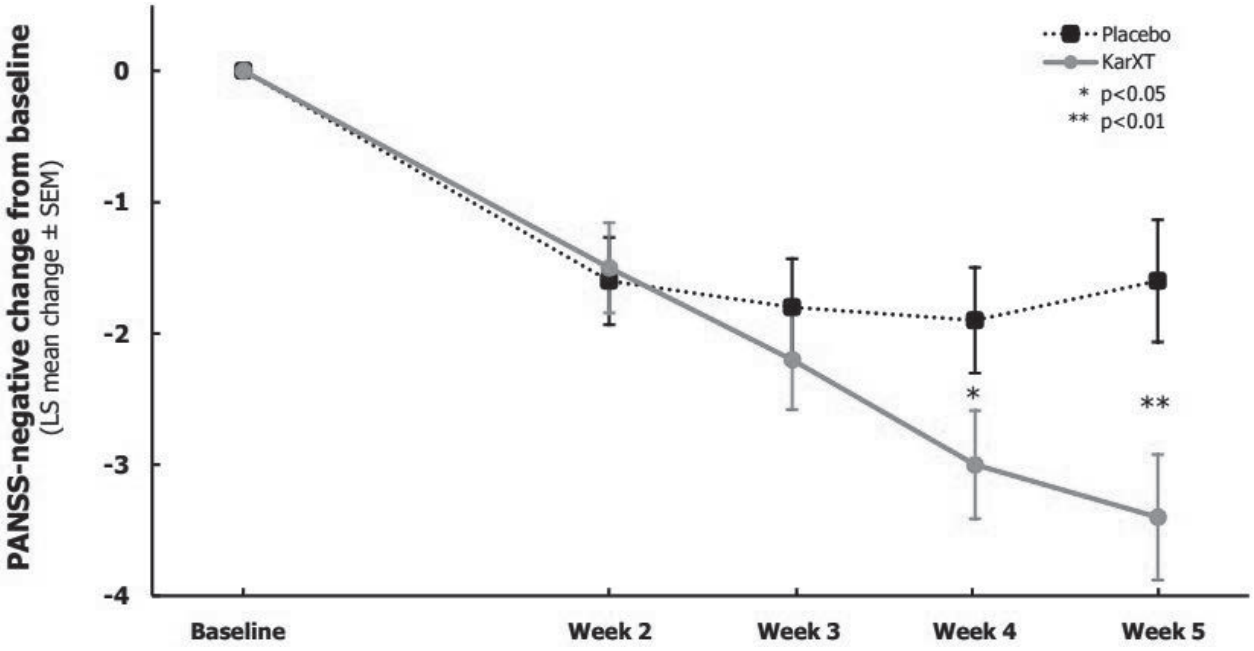
Effect of KarXT on PANSS Total Score (EMERGENT-2)



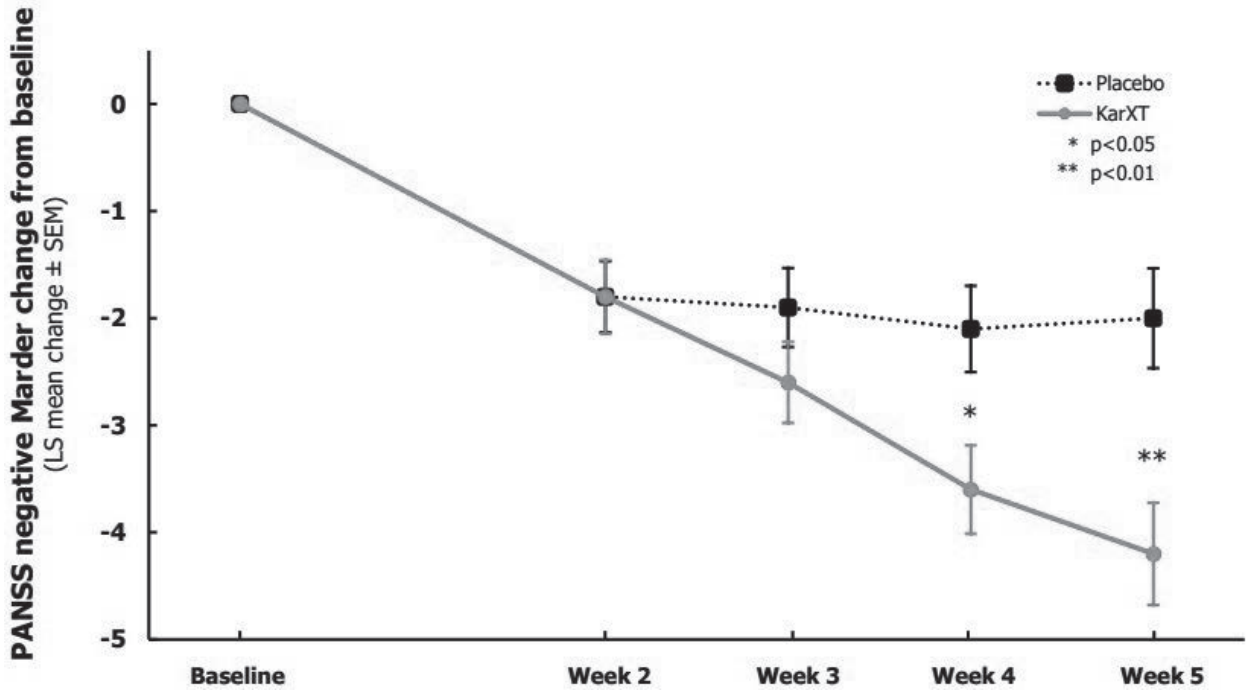
Effect of KarXT on PANSS-positive subscale (EMERGENT-2)



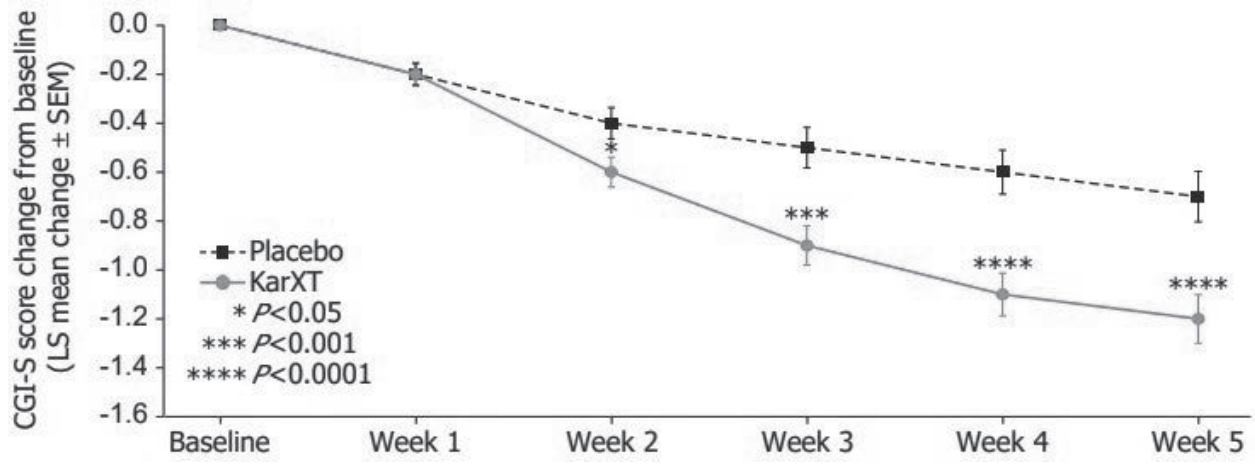
Effect of KarXT on PANSS-negative subscale (EMERGENT-2)



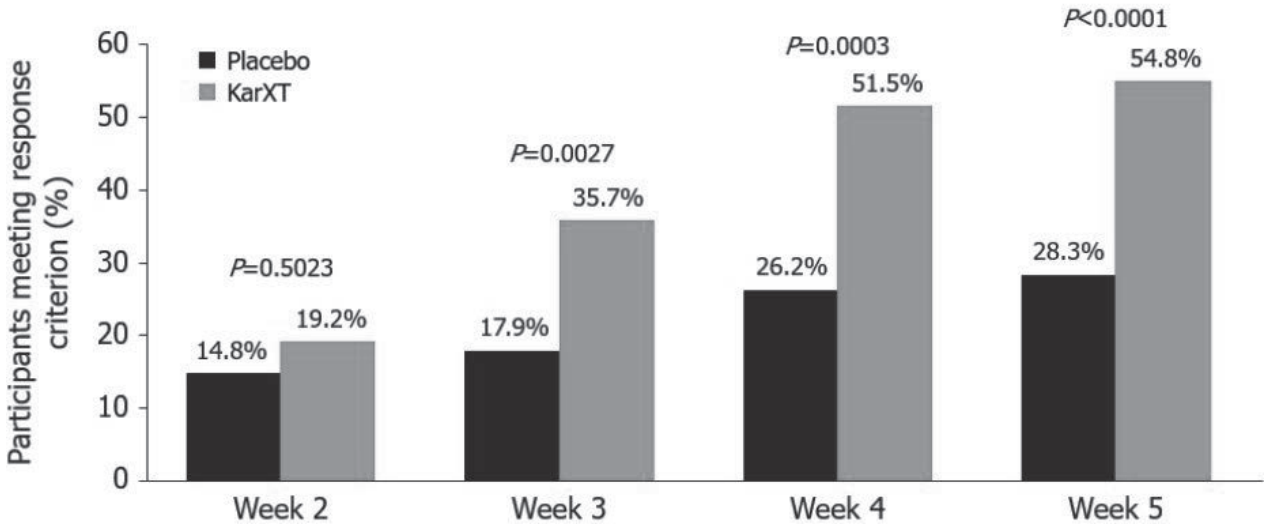
Effect of KarXT on PANSS-negative Marder factor subscale (EMERGENT-2)



Change from baseline in CGI-S score vs placebo at Week 5 (EMERGENT-2)



PANSS ≥30% Categorical Response by Study Week (EMERGENT-2)



KarXT was generally well tolerated in this trial. Overall discontinuation rates were similar between KarXT and placebo groups (25% vs. 21%). The overall rate of TEAEs for KarXT and placebo was 75% and 58%, respectively. Discontinuation rates related to TEAEs were similar between KarXT (7%) and placebo (6%). Equal rates of serious TEAEs were observed between KarXT and placebo (2% in each group) and included suicidal ideation, worsening of schizophrenia symptoms, and appendicitis. None of the serious TEAEs were determined to be drug related. The most common TEAEs (≥5%) in the KarXT arm were all mild to moderate in severity and included constipation, dyspepsia, nausea, vomiting, headache, hypertension, dizziness, gastroesophageal reflux disease (acid reflux), abdominal discomfort, and diarrhea. Mean blood pressure measures were similar between KarXT and placebo throughout the trial, and no syncopal events were observed. In the subset of patients with a TEAE of hypertension, mean blood pressure at endpoint was similar to baseline and did not lead to trial discontinuation. Similar to prior trials, an increase in heart rate was associated with KarXT treatment and decreased in magnitude by the end of the trial. Consistent with EMERGENT-1, KarXT was not associated with common problematic side effects of current treatments, including sedation (somnolence), weight gain, and extrapyramidal symptoms. In the trial, 81% of patients on KarXT compared to 90% on placebo titrated to the highest dose level.

Our Additional EMERGENT Clinical Trials and NDA Plans

Following the positive results of EMERGENT-1, we had an End-of-Phase 2 meeting with the FDA in which the FDA indicated 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 submission in schizophrenia. As a result of the recently completed EMERGENT-2 trial, we plan to submit our NDA to the FDA in mid-2023. If approved, we are targeting a potential commercial launch of KarXT for the treatment of schizophrenia in the second half of 2024.

In addition to our completed Phase 2 EMERGENT-1 and Phase 3 EMERGENT-2 trials, our EMERGENT program that is evaluating KarXT for the treatment of schizophrenia as a monotherapy includes the following Phase 3 trials:

- EMERGENT-3: A five-week inpatient trial evaluating the efficacy and safety of KarXT compared to placebo in 256 adults with schizophrenia, conducted in the United States and Ukraine. We completed enrollment of EMERGENT-3 in the fourth quarter of 2022 and we anticipate topline data in the first quarter of 2023.
- EMERGENT-4: 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. Enrollment for this trial completed in the fourth quarter of 2022.
- EMERGENT-5: A 52-week outpatient, open-label trial conducted in the United States and Puerto Rico evaluating the long-term safety and tolerability of KarXT in adults with schizophrenia who were not enrolled in EMERGENT-2 or EMERGENT-3. Enrollment for this trial began in the second quarter of 2021.

In addition to the EMERGENT program, we began enrolling patients in November 2022 in the PENNANT trial, a three-year, open-label, outpatient Phase 3b trial evaluating the long-term safety, tolerability and efficacy of KarXT in up to 380 adults with schizophrenia in the United States. For business prioritization purposes, we subsequently discontinued patient enrollment and will not be recruiting further patients into this trial. The decision to discontinue enrollment was not due to study conduct or any result or finding from the trial, or otherwise related to KarXT.

We also plan to initiate a Phase 1B open-label clinical trial to evaluate the effect of KarXT on 24-hour ambulatory blood pressure in adults with schizophrenia early in the second quarter of 2023.

Our Ongoing ARISE Program for KarXT as Adjunctive Therapy in Adults with Schizophrenia

Given the unique mechanism of action of KarXT in comparison to existing standard of care therapies, we believe there is the potential for therapeutic benefit as both a monotherapy and as an adjunctive therapy for the treatment of schizophrenia. In November 2021, we initiated our Phase 3 ARISE trial to evaluate the safety and efficacy of KarXT compared to placebo as an adjunctive treatment in adults with schizophrenia who have an inadequate response to their current antipsychotic therapy. This six-week, 1:1 randomized, double-blind, placebo-controlled Phase 3 outpatient trial is designed to enroll approximately 400 adults with schizophrenia who have not achieved an adequate response to their current atypical antipsychotic treatment, and is being conducted in the United States and Europe. Participants in this trial will continue their currently prescribed atypical antipsychotic therapy at the same dose or regimen schedule as prior to entry in the study, and will receive a flexible dose of KarXT or placebo based on tolerability and clinical response as determined by a clinician. The primary outcome measure of the trial is change in PANSS total score of KarXT compared to placebo at week 6. Upon completion of the trial at week 6, participants have the opportunity to enroll in ARISE-2, an ongoing 52-week outpatient, open-label extension trial evaluating the long-term safety and tolerability of KarXT when dosed with atypical antipsychotic treatment. We anticipate topline data from the ARISE trial in the first half of 2024.

Our Development Plans for KarXT for the Negative and Cognitive Symptoms of Schizophrenia

We are collecting data on the potential benefit of KarXT on negative and cognitive symptoms of schizophrenia as part of the ongoing EMERGENT and ARISE programs, which will help inform future potential development plans specifically directed towards the 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 Phase 2 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.

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 Psychosis in Alzheimer's Disease

Approximately 8.4 million people in the United States are living with dementia. 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. 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.

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. We are studying KarXT in the AD psychosis population as the first indication in our DRP program.

Our Completed 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 utilized 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.

The placebo-controlled, inpatient Phase 1b dose-ranging trial consisted of three cohorts, each enrolling 16 healthy elderly 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 a clinician. In the trial, the majority of healthy elderly volunteers were titrated to xanomeline doses of 150 to 200 mg when dosed with KarXT three times per day. Pharmacokinetic data demonstrated that healthy elderly volunteers achieved mean xanomeline blood levels comparable to the mean xanomeline blood levels reported in the Phase 2 EMERGENT-1 trial evaluating KarXT in adults with schizophrenia. Previous trials of KarXT have demonstrated that the current formulation of KarXT results in xanomeline exposures, or blood levels, that are approximately 10% greater than blood levels seen in earlier trials of xanomeline alone.

The treatment-related adverse events, or AEs, were similar to those observed in prior trials of KarXT, and a majority (>80%) were rated mild in severity. One serious AE of urinary retention was reported in Cohort 1. We believe the report of urinary retention was related to a higher dose of trospium used in Cohort 1 compared to doses used in Cohorts 2 and 3, where urinary retention was not observed. No serious or severe AEs were observed in Cohorts 2 and 3. Consistent with prior trials of KarXT, blood pressure in healthy elderly volunteers receiving KarXT was similar to placebo, and no syncopal events were observed. Heart rate increases observed in the trial were also consistent with prior trials of KarXT.

Data from the Phase 1b trial suggest that a lower dose ratio of trospium to xanomeline, compared to the ratios used in Phase 1 trials in healthy adult volunteers and in the Phase 2 EMERGENT-1 and Phase 3 EMERGENT-2 trials evaluating KarXT in adults with schizophrenia, was better tolerated by healthy elderly volunteers.

Our Ongoing ADEPT program for the Treatment of Psychosis Related to Alzheimer's Disease

The ADEPT program, which is the clinical program evaluating KarXT as a potential treatment for psychosis related to AD, consists of the following ongoing and planned Phase 3 trials:

- ADEPT-1: A trial evaluating the efficacy and safety of KarXT compared to placebo in up to 400 adults with moderate to severe psychosis related to AD. This trial consists of a 12-week, single-blind treatment period, followed by a 26-week, double-blind, randomized withdrawal period in which subjects who meet the response criteria will be randomized to receive KarXT or placebo. The single-blind treatment period is designed to enroll approximately 400 adults with AD, between 55 and 90 years old, with moderate to severe hallucinations or delusions, who are living at home or at an assisted living facility. The primary objective of this trial is to evaluate relapse prevention as measured by time from randomization to relapse during the 26-week, double-blind period. This trial is being conducted in the United States and Europe. Enrollment for this trial began in the third quarter of 2022 and topline data is anticipated in 2025.

- ADEPT-2: A 12-week, flexible-dose, double-blind, placebo-controlled trial evaluating the efficacy and safety of KarXT versus placebo. ADEPT-2 is expected to initiate in the second half of 2023, with topline data anticipated in 2025.
- ADEPT-3: A 52-week open-label extension trial evaluating the long-term safety and tolerability of KarXT in adults with psychosis related to AD who completed ADEPT-1 or ADEPT-2. Enrollment for this trial is anticipated to commence in 2023.

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 and long-acting injectable formulations. In November 2021, we initiated a Phase 1 study of an advanced oral formulation of KarXT, and continue to evaluate the optimal xanomeline to trospium dose ratios, as well as dosing regimens, for advanced oral formulations.

Other Research and Development 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 psychosis in AD. 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 2023. 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. We continue to evaluate other opportunities focused on muscarinic and non-muscarinic targets for CNS disorders.

In January 2023, we entered into an exclusive global license agreement for Goldfinch Bio's TRPC4/5 product candidates, including the lead clinical-stage TRPC4/5 candidate, KAR-2618. KAR-2618 has been dosed in over 100 humans across Goldfinch Bio's clinical trials with a well-tolerated safety profile to date. KAR-2618 has shown promising benefits in preclinical models of mood and anxiety disorders with observed anxiolytic and antidepressant properties. We believe that the TRPC4/5 mechanism could represent a novel approach to treating mood and anxiety disorders and complements our existing pipeline of differentiated potential medicines. We intend to provide details on the planned development of KAR-2618 for the treatment of mood and anxiety disorders in the second half of 2023.

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, clinical, and potential commercial launch 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 ongoing and planned clinical trials, including our EMERGENT, ARISE, ADEPT programs, as well as support our NDA application and potential commercial launch. 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 Esteve Quimica, S.A., for the manufacture of xanomeline and source trospium from Procos, S.p.A. and Midas Pharmaceuticals, Inc. 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

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 and Abilify Maintena, marketed by Otsuka Holdings, Rexulti marketed by Lundbeck, Risperdal Consta, Invega, Invega Trinza and Invega Sustenna, marketed by Johnson & Johnson, Zyprexa, marketed by Eli Lilly, Vraylar, marketed by Abbvie, Clozaril, marketed by HLS Therapeutics, Latuda, marketed by Sumitomo Pharma, Caplyta, marketed by Intra-Cellular Therapies, and Lybalvi, marketed by Alkermes. 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 intended to provide an antipsychotic benefit, including product candidates being developed by Acadia Pharmaceuticals, or Acadia, Sunovion Pharmaceuticals, Roche, Neurocrine Biosciences, SyneuRx, Newron Pharmaceuticals, MapLight Therapeutics, Reviva Pharmaceuticals, Boehringer Ingelheim, Teva Pharmaceuticals, Anavax Life Sciences, Intra-Cellular Therapies, Otsuka Holdings, Alkermes and Cerevel Therapeutics.

There are currently no FDA-approved drugs for the negative or cognitive symptoms of schizophrenia. However, we are aware of companies with product candidates in clinical development for the treatment of the negative and cognitive symptoms of schizophrenia, including Boehringer Ingelheim and Neurocrine Biosciences for cognitive symptoms, and Acadia, Otsuka Holdings, Minerva Neurosciences and Roche for negative symptoms.

Psychosis in Patients with Alzheimer's Disease

There are currently no approved treatments for psychosis related to AD. Patients with AD are commonly treated with antipsychotic medications that are indicated and approved for schizophrenia. In 2020, Acadia submitted an sNDA application for marketing authorization of its drug (currently approved for a different indication) for the treatment of hallucinations and delusions associated with DRP, and the FDA issued a complete response letter in April 2021. Acadia resubmitted this sNDA, for the treatment of hallucinations and delusions associated with dementia focused on AD psychosis, in the first quarter of 2022 and the FDA issued a complete response letter in August 2022. In June 2022, Otsuka Holdings and Lundbeck announced positive Phase 3 results of brexpiprazole (Rexulti) in the treatment of agitation in patients with Alzheimer's dementia, and in January 2023, the FDA accepted the submitted sNDA application. Additionally, we are aware of several product candidates in clinical development that are intended to provide an antipsychotic benefit to patients with AD-related psychosis, including product candidates being developed by Sunovion Pharmaceuticals, BioXcel Therapeutics, Intra-Cellular Therapies, Otsuka Holdings and Lundbeck, Acadia, Axsome Therapeutics, Janssen Pharmaceuticals, Suven Life Sciences, Merck and Cerevel Therapeutics. 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, Novartis and Pfizer.

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

KarXT

We exclusively license KarXT from PureTech Health LLC, or PureTech Health, a patent family that, as of February 15, 2023, comprises 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 CNS 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, Japan and Hong Kong, and a total of five patent applications pending, one in each of the U.S., Europe and Hong Kong, and two in Japan. 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 four issued U.S. patents, issued patents in Australia, Brazil, Canada, Israel, India, Japan, Korea, Mexico, and New Zealand, and one pending U.S. patent application, and a total of 21 pending patent applications in Australia, Canada, Chile, China, Costa Rica, Eurasia, Egypt, Europe, Hong Kong, Indonesia, Israel, Japan, the Philippines, Saudi Arabia, Singapore, Thailand, Ukraine, Vietnam, and South Africa with claims directed towards the KarXT drug product, including claims 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, and related methods of treatment using the KarXT drug product. The patents 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 a total of four pending patent applications, one in each of Canada, China, Europe, and Japan, 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 one pending PCT application and one Taiwanese application, with claims directed towards treating a disorder ameliorated by activating muscarinic receptors in an elderly patient in need thereof using xanomeline and/or a salt thereof and a salt of trospium. The pending patent applications, if issued, are expected to expire in 2042 without taking into account a possible PTE or any possible patent term adjustments.

We also own one pending U.S. patent application, one pending US provisional application, one PCT application, and one European application with claims directed towards treating CNS disorders with xanomeline and/or a salt thereof and an antipsychotic. The pending patent applications, if issued, are expected to expire in 2042 without taking into account a possible PTE or any possible patent term adjustments.

We also own two pending U.S. provisional applications with claims directed towards treating CNS disorders with xanomeline and/or a salt thereof and a second therapeutic agent. The pending patent applications, if issued, are expected to expire in 2043 without taking into account a possible PTE or any possible patent term adjustments.

We also own one issued U.S. patent, one pending U.S. patent application, one pending U.S. provisional application, and a total of six pending applications in Australia, Canada, China, Europe, Japan, and New Zealand 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.

KAR-2618

With respect to KAR-2618, we exclusively license from GFB (ABC), LLC, or GFB, assignee of the assignment estate of Goldfinch Bio, six patent families that are collectively directed to compound KAR-2618, along with formulations, biomarker technology, combination therapy, and methods of use. Our first exclusively licensed patent family from GFB is directed to a genus of TRPC4/5 compounds and methods of use and, as of February 15, 2023, contains one pending U.S. patent application along with patent applications pending in Europe, Hong Kong, Australia, and Canada. Any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2038, without taking into account any patent term adjustment, PTE, or supplementary protection certificate, or SPC.

Our second exclusively licensed patent family from GFB describes KAR-2618 and methods of use and, as of February 15, 2023, contains two U.S. patents, one pending U.S. patent application, and patent applications pending in Europe, Japan, Australia, Canada, China, and over 20 additional foreign countries. These U.S. patents, and any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2039, without taking into account any patent term adjustment, PTE, or SPC.

Our third patent family exclusively licensed from GFB is directed to polymorphic forms of KAR-2618 and methods of use and, as of February 15, 2023, contains one pending U.S. patent application and patent applications pending in Europe, Japan, Australia, Canada, China, and two additional foreign countries. Any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2040, without taking into account any patent term adjustment, PTE, or SPC.

Our fourth patent family exclusively licensed from GFB is directed to formulations containing KAR-2618 and methods of use thereof and, as of February 15, 2023, contains one pending U.S. patent application and patent applications pending in Europe, Japan, Australia, Canada, China, and over five additional foreign countries. Any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2040, without taking into account any patent term adjustment, PTE, or SPC.

Our fifth patent family exclusively licensed from GFB is directed to combination therapy using KAR-2618 and, as of February 15, 2023, contains one pending U.S. patent application and patent applications pending in Europe, Japan, Australia, Canada, China, and over five additional foreign countries. Any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2040, without taking into account any patent term adjustment, PTE, or SPC.

We also exclusively licensed from GFB a patent family directed to biomarker technology and certain methods of use, which, as of February 15, 2023, contains one pending U.S. patent application and patent applications pending in Europe, Japan, Australia, Canada, China, and over 15 additional foreign countries. Any U.S. or foreign patents that issue based on the pending patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2040, without taking into account any patent term adjustment, PTE, or SPC.

Additionally, with respect to KAR-2618, as of February 15, 2023, we solely own two pending U.S. provisional patent applications directed to methods of use. Any U.S. or foreign patents that issue from a non-provisional patent application filed in the future based on these provisional patent applications, if granted and if all appropriate maintenance fees are paid, are expected to expire in year 2042, without taking into account any patent term adjustment, PTE, or SPC.

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. As of December 31, 2022, no regulatory or commercial milestones have been reached and, accordingly, no milestone payments have been made.

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 PureTech 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 CNS disorders.

In connection with the PureTech 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. As of December 31, 2022, no other milestone payments have been made under the PureTech License 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 PureTech License Agreement. In the event that we sublicense any of the patent rights granted under the PureTech 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 paid less than $0.1 million in sublicense income associated with the Zai License Agreement to PureTech Health in 2021. As of December 31, 2022, no other royalty payments have been made under the PureTech License Agreement.

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

License Agreement with Zai Lab

In November 2021, we entered into a License Agreement, or the Zai License Agreement, with Zai Lab (Shanghai) Co., Ltd, or Zai, pursuant to which we granted to Zai the right to exclusively develop, manufacture and commercialize KarXT in mainland China, Hong Kong, Macau, and Taiwan, referred to as the Licensed Territory.

Under the terms of the Zai License Agreement, we received a $35 million upfront payment and are eligible to receive total development and regulatory milestone payments of up to an additional $80 million. As of December 31, 2022, we have received $10 million of the potential $80 million in development and regulatory milestone payments under the Zai License Agreement. We are also eligible to receive total sales milestone payments up to $72 million and low double-digit to high-teens tiered royalties based on annual net sales of KarXT in the Licensed Territory, subject to reduction under specified circumstances. Zai will fund substantially all development, regulatory, and commercialization activities in the Licensed Territory.

The Zai License Agreement will expire upon the latest of the following dates with respect to the last licensed product in any region in the Licensed Territory: (i) the date of expiration of the last valid claim covering such licensed product in such region, (ii) the date that is a specific period after the date of the first commercial sale of such licensed product in such region and (iii) the expiration date of any regulatory exclusivity for such licensed product in such region. Subject to the terms of the Zai License Agreement, Zai may terminate the Zai License Agreement for convenience by providing written notice to us, which termination will be effective following a prescribed notice period. In addition, we may terminate the Zai License Agreement under specified circumstances if Zai or certain other parties challenge our patent rights or if Zai or its affiliates fail to complete certain development activities with respect to the licensed product for a specified period of time, subject to specified exceptions. Either party may terminate the Zai License Agreement for the other party's uncured material breach of the Zai License Agreement, with a customary notice and cure period, or insolvency. After termination or expiration of the Zai License Agreement, we are entitled to retain a worldwide, exclusive, and perpetual license from Zai to exploit the licensed product (which license would be non-exclusive after expiration (but not termination) of the Zai License Agreement), subject to a reasonable royalty to be agreed by the parties if the Zai License Agreement is terminated for our uncured material breach.

License Agreement with GFB

In January 2023, we entered into an exclusive license agreement, or the GFB License Agreement, with GFB, assignee of the assignment estate of Goldfinch Bio, pursuant to which GFB granted us the exclusive right and license to develop, manufacture, and commercialize GFB's TRPC4/5 candidates, or the GFB Compounds, including the lead clinical-stage candidate known as KAR-2618 (formerly GFB-887). We agreed to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize at least one licensed product that contains or comprises a GFB Compound in at least two indications in the United States.

Under the terms of the GFB Agreement, we paid to GFB a $15 million upfront payment, and agreed to pay a total of up to $520 million for each GFB Compound upon the achievement of certain development, regulatory and commercial milestones with respect to such GFB Compound, of which $110 million, $150 million, and $260 million are related to development, regulatory, and commercial sales milestones, respectively. We also agreed to pay GFB a flat low-single digit royalty on aggregate net sales of each licensed product on a country-by-country basis until the expiration of the applicable royalty term, which ends on the later of (i) the expiration date of the last valid claim covering the licensed product in such country, (ii) the expiration date of regulatory exclusivity with respect to such licensed product in such country, and (iii) the date that is a specific period after the first commercial sale of such licensed product in such country. The royalty rate is subject to reduction on a licensed product-by-licensed product and country-by-country basis under certain circumstances. In the event that we sublicense to a third party any of the rights to the licensed intellectual property granted under the GFB License Agreement, we will be obligated to pay GFB royalties within the range of 25% to 35% on any consideration we receive from the sublicensee, excluding royalties and certain other payments.

Unless earlier terminated, the GFB Agreement will expire on the expiration of the last to expire royalty term. Unless the GFB Agreement is earlier terminated, on expiration of each applicable royalty term, we will have a fully paid-up, irrevocable and perpetual license to develop, manufacture and commercialize each applicable licensed product in the applicable country. Either party may terminate the GFB Agreement for the other party's material breach, following a customary notice and cure period, or insolvency. We may terminate the GFB Agreement for any reason upon 90 days written notice to GFB.

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 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 obtaining 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.

Post-approval, or Phase 4, 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. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of approval for a product granted accelerated approval. Sponsors are also required to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. 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. In addition, the FDA generally requires, unless otherwise informed by the agency, pre-approval of promotional materials for product candidates approved under accelerated approval, which could adversely impact the timing of the commercial launch of the product.

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, the FDA will only issue an approval letter when the deficiencies have been addressed to the FDA's satisfaction. 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, tracking and tracing requirements, 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 five 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

In April 2014, the European Union adopted the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation), which replaced the Clinical Trials Directive 2001/20/EC on 31 January 2022. The Clinical Trials Regulation is directly applicable in all the EU Member States, meaning national implementing legislation in each EU Member State is not required. The transitory provisions of the new Clinical Trials Regulation provide that, by January 31, 2025, all ongoing clinical trials must have transitioned to the new Clinical Trials Regulation.

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 through the Clinical Trials Information System, or CTIS; 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 contains scientific and medicinal product documentation and Part II contains the national and patient-level documentation). 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) of a draft report prepared by a Reference Member State. 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 Clinical Trials Directive 2001/20/EC into national law through the Medicines for Human Use (Clinical Trials) 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, however the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, has opened a consultation on a set of proposals designed to improve and strengthen the UK clinical trials legislation. Such consultation ran from January 17, 2022 to March 14, 2022, and the MHRA is currently analyzing feedback.

Marketing Authorization

To obtain a marketing authorization for a product in the European Union, 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 in the additional Member States of the European Economic Area (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 medicinal products (gene-therapy, somatic cell-therapy or tissue-engineered medicines), 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 constitute 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 by the EMA 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 asked by the CHMP. Clock stops may extend the timeframe of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, it provides the opinion together with supporting documentation to the European Commission, who makes the final decision to grant a marketing authorization, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be 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, excluding clock stops, 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.

Unlike the centralized procedure, the decentralized 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 EU Member States of the make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety, and efficacy.

Now that the United Kingdom has left the European Union, Great Britain is no longer covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized EU authorizations 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 three years from January 1, 2021, the 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. On January 24, 2023, the MHRA announced that a new international recognition framework will be put in place from January 1, 2024, which will have regard to decisions on the approval of marketing authorizations made by the EMA and certain other regulators. The MHRA also has the power to have regard to marketing authorizations approved in EU Member States through the decentralized or mutual recognition procedures a view to more quickly granting a marketing authorization in the United Kingdom or Great Britain.

Data and Market Exclusivity in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete and 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 with the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic marketing authorization in the European Union, during a period of eight years from the date on which the reference product was first authorized in the European Union. 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 EU 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. There is no guarantee that a product will be considered by the EMA to be an innovative medicinal product, and products may not qualify for data exclusivity. Even if a product is considered to be an innovative medicinal product 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 for a nationally authorized product. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period, unless the European Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the authorizing EU Member State (for a nationally authorized product) within three years after authorization ceases to be valid (the so-called sunset clause).

Regulatory Requirements after a Marketing Authorization has been Obtained

If 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 EU 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 EU 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. Direct-to-consumer advertising of prescription medicines is prohibited across the European Union.

The aforementioned European Union rules are generally applicable in the European Economic Area, or EEA, which consists of the EU Member States, plus Norway, Liechtenstein and Iceland.

European General Data Protection 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 data including health information in the European Union is governed by the provisions of the General Data Protection Regulation, or GDPR, as well as national data protection laws. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, such as including requirements relating to having legal bases for processing personal data relating to identifiable individuals and transferring such information outside the EEA, including to the United States (see below), providing details to those individuals regarding the processing of their personal data, implementing safeguards to keep personal data secure, having data processing agreements with third parties who process personal data, providing information to individuals regarding data processing activities, responding to individuals' requests to exercise their rights in respect of their personal data, obtaining consent of the individuals to whom the personal data relates, reporting security and privacy breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR allows for penalties to which we could be subject in the event of any non-compliance, including fines of up to €20,000,000 or 4% of total annual global revenue, whichever is greater. The GDPR imposes 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, the United Kingdom incorporated the GDPR (as it existed on December 31, 2020 but subject to certain UK specific amendments) into UK law, or UK GDPR, following its exit from the EU in 2020. 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. The UK Government has announced plans to reform the data protection legal framework in its Data Reform Bill but those have been put on hold. 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. Although the United Kingdom is regarded as a third country under the EU's GDPR, the European Commission has now issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the European Union to the United Kingdom remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the United Kingdom as providing adequate protection. The UK government has confirmed that personal data transfers from the United Kingdom to the EEA remain free flowing.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom formally left the European Union on January 31, 2020, and the European Union and the United Kingdom have concluded a trade and cooperation agreement, or the TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework continues to apply in Northern Ireland). The regulatory regime in Great Britain therefore aligns in many ways with current EU regulations, however it is possible that these regimes will diverge significantly in the future now that Great Britain's regulatory system is independent from the European Union and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation.

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:

- **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. Effective January 19, 2021, the Office of Inspector General, or OIG, added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others;
- **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, 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 Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively 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 were extended to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- **Price Reporting Laws**— Federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;
- **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;

- **California Privacy Rights Act (CPRA)** – The CPRA established a 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 exempt from the CPRA, other personal information may be applicable. In addition to the CPRA, new privacy and data security laws have been proposed in more than half of the states in the United States and in the U.S. Congress, reflecting a trend toward more stringent privacy legislation in the United States. The effects of the CPRA, and other similar state or federal laws, are potentially significant and may require us to modify our data processing practices and policies and to incur substantial costs and potential liability in an effort to comply with such legislation; 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 GDPR, 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 in recent 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, or the ACA, which, among other things, includes contains to the coverage and payment for products under government health care programs. The ACA 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.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative efforts to expand, repeal, replace or modify the ACA, some of which have been successful, in part, in modifying the law, as well as court challenges to the constitutionality of the law. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business.

In addition, other legislative and regulatory changes have been proposed and adopted in the United States since the ACA was enacted:

- On August 2, 2011, the U.S. Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. Following the temporary suspension, a 1% payment reduction began April 1, 2022, lasting through June 30, 2022. The 2% payment reduction resumed on July 1, 2022.
- On January 2, 2013, the U.S. American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers.
- On April 13, 2017, CMS published a final rule that gives states greater flexibility 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.
- On May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.
- On May 23, 2019, CMS published a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020.
- On December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repealed 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.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. At a federal level, President Biden signed an Executive Order on July 9, 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. FDA released such implementing regulations 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. On September 25, 2020, CMS stated drugs imported by states under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for "best price" or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a National Average Drug Acquisition Cost for these drugs. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. 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 would have been 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. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule.

Additionally, on November 30, 2020, HHS published 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. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. The Inflation Reduction Act of 2022, or the IRA, further

delayed implementation of this rule to January 1, 2032. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

In August 2022, the IRA was signed into law. The IRA includes several provisions that will impact our business to varying degrees, including provisions that create a $2,000 out-of-pocket cap for Medicare Part D beneficiaries, impose new manufacturer financial liability on all drugs in Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D pricing for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for drug prices that increase faster than inflation, and delay the rebate rule that would require pass through of pharmacy benefit manager rebates to beneficiaries. The effect of IRA on our business and the healthcare industry in general is not yet known.

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. EU 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 EU 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 99 High Street, Floor 26, Boston, Massachusetts, where we occupied approximately 25,443 square feet of leased office space as of December 31, 2022. This lease expires in December 2025.

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.

Human Capital

We believe that our employees are critical to the success of our mission, and that our future success will depend in large part on our continued ability to attract, hire and retain qualified personnel. We continuously strive to ensure that employee morale remains strong, and conduct employee engagement satisfaction surveys and monitor employee turnover rates as part of this process.

As of February 15, 2023, we had 210 full-time employees, including a total of 50 employees with M.D. and/or Ph.D. degrees. Of our workforce, 142 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.

Diversity, Equity and Inclusion

We are committed to cultivating and preserving a culture of diversity, equity and inclusion, and aim to foster an inclusive environment through respect, collaboration, and open communication. We embrace and encourage the differences among our employees that make them unique, and believe that these differences, as well as corresponding diversity of opinions and thought, contribute to our success as a company. During 2022, we established an employee-led committee dedicated to diversity, equity and inclusion at Karuna. As we grow and mature, we will continue to implement initiatives to foster the diversity and inclusiveness of our workforce, and to ensure that employees of all backgrounds can thrive at Karuna.

Compensation and Benefits

To ensure our compensation and benefits programs are competitive, we engage a nationally recognized outside compensation and benefits consulting firm to independently evaluate the effectiveness of our programs and to provide benchmarking against our peers within the industry. Our pay-for-performance philosophy seeks to motivate and reward employees while accomplishing the Company's short and long-term strategic goals. As part of a robust performance management process, employees are evaluated both on what they accomplished and how they demonstrated our core competencies. Annual salary increases and incentive bonuses are based on merit and include individual and corporate performance factors.

We offer robust compensation packages, including competitive base pay, incentive compensation and equity programs, and provide a broad range of benefits, including 401(k) plan, healthcare and insurance benefits, a health savings account, paid time off, paid family and medical leave, and various health and wellness programs. Through our equity incentive plan, we aim 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. In addition, we are committed to the professional development of our employees, who can take advantage of various learning opportunities and training programs.

Health, Wellness and Safety

Employee safety and well-being is very important to us, particularly in light of COVID-19. In response to the pandemic, we have taken extra precautions to reduce the risk of virus exposure for our employees. We implemented a work from home policy for all employees who are able to perform their duties remotely, and we provide protective equipment for those of our employees working on site. We have also implemented and continue to adapt safety protocols and procedures to ensure compliance with local, state and federal guidelines, as well as to keep the members of our workforce healthy and safe. For our remote employees, we provide collaboration tools and resources and support their information technology needs. Aligned with our mission and to support our employees' mental health, we introduced an offering of online resources to assist with professional and financial coaching, wellness courses, and therapy services.

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 99 High Street, Floor 26, 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 a significant portion 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 $276.3 million, $143.8 million and $68.6 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $564.2 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, and prepare for potential commercialization.

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 KAR-2618 (formerly GFB-887) and 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 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, including KAR-2618. 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 existing or 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 our existing or future collaborators may never succeed in these activities and, even if we, or any existing or 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.

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, licensing our technology, conducting research and development activities, including preclinical studies and clinical trials, for our product candidates, and preparing for potential commercialization. We have not yet demonstrated an ability to generate product 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 are in the process of transitioning from a company with a development focus to a company capable of supporting commercial activities, and may not be successful in such a transition.

We may 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 costs are not the responsibility of a collaborator. 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, including KAR-2618;
- 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 an existing or future collaborator, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to the receipt of regulatory approval, revenue, if any, received from commercial sales of KarXT, KAR-2618, or any other product candidate we may develop and pursue, for any approved indications;
- 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 commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, and 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 one or more 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, 2022 will be sufficient to meet our anticipated operating and capital expenditure requirements through the end of 2025. 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, including 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.

At December 31, 2022 we had federal net operating loss carryforwards totaling $406.5 million, of which $9.8 million begin to expire in 2029 and $396.7 million can be carried forward indefinitely. In addition, we had state net operating loss carryforwards totaling $321.5 million which begin to expire in 2030. We also had federal and state research and development tax credit carryforwards of $34.9 million and $4.9 million which begin to expire in 2031. Because we had historically been a subsidiary of PureTech, $406.0 million and $301.5 million of the federal and state net operating loss carryforwards, respectively, can be used to offset income on our future tax returns. In addition, $34.8 million and $4.9 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 assessed our potential Section 382 limitations during the year ended December 31, 2022, and while certain tax attributes are subject to annual limitations, none are expected to be restricted in their future utilization if we earn 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; 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. For example, in August 2022, the United States enacted the Inflation Reduction Act, which implemented a 15% minimum tax on book income for certain companies and introduced a 1% excise tax on stock buybacks. 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 psychosis related to Alzheimer's disease, or ADP. 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 ADP, 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;
- receipt and maintenance of marketing approvals from applicable regulatory authorities;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for KarXT;
- making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of KarXT;
- maintaining existing collaborations and entry into new collaborations to further the development of KarXT;
- establishing sales, marketing and distribution capabilities and commercial launch of KarXT, if and when approved, whether alone or in collaboration with others;
- successful commercial launch of KarXT, if and when approved;
- acceptance of KarXT, 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 KarXT 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 existing or future collaborator. If we or any collaborator are unable to develop, receive regulatory approval for, or successfully commercialize KarXT for our initial or potential additional indications, 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 an 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.

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 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 trials, 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 and our collaborators may 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, neither we nor our collaborator have submitted an NDA to the FDA or similar drug approval submissions to comparable foreign regulatory authorities for KarXT, nor have we submitted an NDA for any other product candidate. We, and any existing or 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. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate.

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 our current or 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 existing 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 a 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 ongoing Phase 3 EMERGENT clinical trials of KarXT for the treatment of psychosis in patients with schizophrenia, our ongoing Phase 3 ARISE or ADEPT programs, 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 of KarXT in other indications. We do not know whether any clinical trials that we are conducting or may conduct will demonstrate adequate efficacy and safety to result in regulatory approval to market KarXT, or any other product candidate, for our initial or potential additional indications. If later stage clinical trials do not produce favorable results, our ability to obtain regulatory approval for KarXT for our 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.

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 acquired rights to xanomeline from Eli Lilly and Company, or Eli Lilly, in 2012. More recently, we acquired rights to our investigational transient receptor potential canonical 4 and 5 (TRPC4/5) channel candidates, including the lead clinical-stage candidate, KAR-2618, from the assignment estate of Goldfinch Bio, Inc., or Goldfinch Bio, in 2023. We have relied on Eli Lilly and Goldfinch Bio 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 KAR-2618, respectively, 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 or KAR-2618 prove to be unreliable, this could result in increased costs and delays in the development of KarXT or KAR-2618, as applicable, which could adversely affect any future revenue from such 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 of such product candidates, if ever, and our ability to generate revenues from such product candidates may be delayed.

The results to date of our preclinical studies and clinical trials do not guarantee that we will succeed in developing KarXT or any other product candidate into a marketable product. Initial data in our clinical trials may not be predictive of results obtained when these trials are completed or in subsequent trials.

The results of preclinical studies or clinical trials of our product candidates may not be predictive of the results we or our collaborators may obtain from subsequent clinical trials of the same product candidate. For example, the positive results seen in our Phase 3 EMERGENT-2 trial may not be predictive of future results of our EMERGENT-3 trial or any subsequent clinical trials in our EMERGENT program.

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 experienced significant setbacks in clinical development even after achieving promising results in earlier-stage trials, and any such setbacks in our clinical development could have a material adverse effect on our business and operations.

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 pandemic;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials;

- 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.

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 dementia-related psychosis, or 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 were not able to announce topline results from this trial until the second quarter of 2021. In 2021, we initiated our EMERGENT-3 clinical trial evaluating the efficacy and safety of KarXT compared to placebo in 256 adults with schizophrenia in the United States and Ukraine. Topline results for this trial were expected by the end of 2022. Due to the escalating conflict in Ukraine, in February 2022 we withdrew guidance for EMERGENT-3 and, as a result of not enrolling additional patients in Ukraine, delayed the expected release of topline results from this trial until the first quarter of 2023.

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, 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. We are currently exploring other formulations and modes of administration for KarXT, and to the extent we do the same for KAR-2618 or any future product candidate, such changes carry the risk that KarXT, KAR-2618 or such other product candidates will perform differently and could affect the results of clinical trials conducted with the modified product candidate. 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, KAR-2618 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. In clinical trials of xanomeline, treatment was associated with transient increases in heart rate and liver function tests, both of which returned to baseline with continued treatment, and syncope. Electrocardiograms showed no clinically meaningful changes in cardiac conductivity, including QTc interval. In completed KarXT trials to date, we have not observed any other cardiac effects or liver function test results that are significantly different from placebo, and we have not observed any syncope associated with KarXT treatment. Similar to xanomeline, KarXT has been associated with an increase in heart rate across our trials, which decreased in magnitude toward the end of those trials. While KarXT was associated with a higher rate of reported treatment-emergent adverse events, or TEAEs, of hypertension compared to placebo in our Phase 3 EMERGENT-2 trial, mean blood pressure at endpoint was similar to baseline amongst the subset of patients with this TEAE and did not lead to trial discontinuation.

However, there can be no guarantee that we would observe a similar tolerability profile of KarXT in our ongoing or planned Phase 3 clinical trials or in other future clinical trials. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. 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.

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.

We have concentrated our research and development efforts on the treatment of psychiatric and neurological conditions, a field that faces certain challenges in drug development.

We have focused our research and development efforts on the treatment of psychiatric and neurological conditions. Efforts by biotechnology and pharmaceutical companies in this field have faced certain challenges in drug development. In particular, clinical trials focused on many neuroscience diseases such as schizophrenia or ADP rely on subjective patient-reported outcomes as key endpoints. This makes them more difficult to evaluate than indications with more objective endpoints. Furthermore, these indications are often subject to a placebo effect, which may make it more challenging to isolate the beneficial effects of our product candidates. There can be no guarantee that we will successfully overcome these challenges in our ongoing or any future clinical trials of our product candidates or that we will not encounter other challenges in the development of our product candidates.

Even if KarXT, KAR-2618 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, including KAR-2618, 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. Many of the indications for our product candidates have well-established standards of care that physicians, patients and payors are familiar with and, in some cases, are available generically. Even if approved, KarXT, KAR-2618, or any other future product candidate of ours may not be successful in displacing these current standards of care if we are unable to demonstrate superior efficacy, safety, ease of administration, or cost-effectiveness. For example, 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, including comparable foreign regulatory authorities, 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 of 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, KAR-2618 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, such as KAR-2618, 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 ADP 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, including KAR-2618. 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, such as KAR-2618, as well as commercial products to treat patients suffering from other disorders with significant unmet medical needs and limited treatment options. KAR-2618 and 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 their potential for regulatory approval, unmet need and potential commercial success. 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, including through entering into 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, KAR-2618 for mood and anxiety disorders, 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, KAR-2618 for mood and anxiety disorders, 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 or KAR-2618 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 or other product candidates 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 positive, or psychotic, symptoms of schizophrenia. These drugs include: Abilify and Abilify Maintena, marketed by Otsuka Holdings, Rexulti marketed by Lundbeck, Risperdal Consta, Invega, Invega Trinza and Invega Sustenna, marketed by Johnson & Johnson, Zyprexa, marketed by Eli Lilly, Vraylar, marketed by Abbvie, Clozaril, marketed by HLS Therapeutics, Latuda, marketed by Sumitomo Pharma, Caplyta, marketed by Intra-Cellular Therapies, and Lybalvi, marketed by Alkermes.

Similarly, while there are currently no FDA-approved treatments for DRP, including psychosis related to Alzheimer's Disease, or AD, patients with DRP are commonly treated with antipsychotic medications that are indicated and approved for schizophrenia. In 2020, Acadia submitted an sNDA application for marketing authorization of its drug (currently approved for a different indication) for the treatment of hallucinations and delusions associated with DRP, and the FDA issued a complete response letter in April 2021. Acadia resubmitted this sNDA, for the treatment of hallucinations and delusions associated with dementia focused on AD psychosis, in the first quarter of 2022 and the FDA issued a complete response letter in August 2022. 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, Novartis and Pfizer.

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. For example, we are aware of several product candidates in clinical development that are intended to provide an antipsychotic benefit, including product candidates being developed by Acadia, Sunovion Pharmaceuticals and Cerevel Therapeutics. We are also aware of companies with product candidates in clinical development for the treatment of the negative and cognitive symptoms of schizophrenia, including Boehringer Ingelheim and Neurocrine Biosciences for cognitive symptoms, and Acadia Minerva Neurosciences and Roche for negative symptoms.

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. 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, and 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. 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. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates.

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 qualified scientific and management personnel and establishing clinical trial sites, as well as in acquiring technologies complementary to, or necessary for, our programs. Our competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan.

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.

Karuna has several patents and pending patent applications directed to combinations of xanomeline and trospium chloride. These patents, however, 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. While we believe the FDA will treat the xanomeline in KarXT as an NCE, which would afford us with five years of NCE data exclusivity if approved, if it does not, the FDA may approve generic versions of KarXT 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 limited 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 limited 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 or DRP, we intend to expand our commercial capabilities, 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, marketing and market access personnel;

- the inability of sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe any future products;
- 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 or our collaborators are not successful in commercializing any approved products, our future product revenue will suffer and we may incur significant additional losses.

Any of our current and future product candidates for which we, or any existing or 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 and limit how we or such collaborators manufacture and market our products, which could impair our ability to generate revenue. If we or such collaborators fail to comply with applicable regulatory requirements or experience unanticipated problems with any product following approval, we or such collaborators may be subject to substantial penalties.

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 existing or future collaborators, must therefore comply with requirements concerning, among other things, manufacturing, labeling, packaging, storage, advertising, promotion, sampling, quality control, quality assurance and corresponding record-keeping, conduct of post-marketing studies and submission of safety, efficacy and other post-market information for any of our product candidates for which we or they obtain regulatory approval.

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. Accordingly, assuming we, or any existing or future collaborators, receive regulatory approval for one or more of our product candidates, we, or any collaborators, and our or 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. 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.

Any regulatory approvals that we or our collaborators receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the product candidate. Certain endpoint data we hope to include in any approved product labeling, including exploratory or secondary endpoint data such as patient-reported outcome measures, may not be included by the FDA in the approved product labeling. The FDA may also require a risk evaluation and mitigation strategies, or REMS, program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

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 existing or future collaborators will not be able to promote any products we develop for indications or uses for which they are not approved. 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.

If we, and any existing or future collaborators, are not able to comply with post-approval regulatory requirements, we, and any collaborators, could have the regulatory approvals for our products withdrawn by regulatory authorities and our, or any 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. 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 have additional consequences, 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;
- 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.

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 collaborators 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.

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 in the future, if approved, 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 product candidates or 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.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, 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. Healthcare laws and regulations may also 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. In addition, transparency laws and patient privacy laws can apply to the activities of pharmaceutical manufacturers. Restrictions under applicable federal and state healthcare laws and regulations include those described in the section of this Annual Report on Form 10-K entitled, "Business — Healthcare and Privacy Laws and Regulation".

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, which could adversely affect or business or operations.

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 also generally not permitted in the countries that form part of the European Union. Some European Union Member States, and the United Kingdom, through the United Kingdom Bribery Act 2010, have enacted laws explicitly prohibiting the provision of these types of benefits and advantages to induce or reward improper performance generally. Infringements of these laws can result in substantial fines and imprisonment. EU Directive 2001/83/EC, which is the EU Directive governing medicinal products for human use, further provides that, where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy. This provision has been transposed into the Human Medicines Regulations 2012 and so remains applicable in the United Kingdom despite its departure from the European Union.

Payments made to healthcare providers 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.

Our business is subject to complex and evolving U.S. and foreign laws and regulations, information security policies and contractual obligations relating to privacy and data protection, including the use, processing, and cross-border transfer of personal information. These laws and regulations are subject to change and uncertain interpretation, and could result in claims, changes to our business practices, or monetary penalties, and otherwise may harm our business.

We receive, generate and store significant and increasing volumes of sensitive information and business-critical information, including employee and clinical trial subject personal data (including protected health information), research and development information, commercial information, and business and financial information. We heavily rely on external security and infrastructure vendors to manage our information technology systems and data centers. We face a number of risks relative to protecting this critical information, including the loss of access, inappropriate use or disclosure, inappropriate modification, and the risk of our being unable to adequately monitor, audit and modify our controls over our critical information. This risk extends to third-party vendors and subcontractors we use to manage this sensitive data.

A wide variety of provincial, state, national, and international laws, and regulations apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data. These data protection and privacy-related laws and regulations are evolving and may result in ever-increasing regulatory and public scrutiny and escalating levels of enforcement and sanctions. For example, the collection and use of personal data in the European Union are governed by the EU General Data Protection Regulation, or the GDPR. The GDPR imposes stringent data protection requirements, including, for example, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention of information, increased requirements pertaining to special categories of data, such as health data, and additional obligations when we contract with third-party processors in connection with the processing of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the European Union to the United States and other third countries where the protection of personal data of individuals is not as astringent as the GDPR. In the context of clinical trials, we currently rely on patient informed consent as the legal basis for such transfers as well as Standard Contractual Clauses issued and pre-approved by the European Commission that are executed with the parties that we exchange personal data with. In addition, the GDPR provides that EU Member States may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data. The GDPR provides for penalties for noncompliance of up to the greater of €20 million or four percent of worldwide annual revenues. The GDPR applies extraterritorially, and we may be subject to the GDPR with respect to any data processing activities that involve the personal data of individuals located in the European Union, such as in connection with any clinical trials that we may perform in the European Union, including our ARISE and ADEPT clinical trials. GDPR regulations may impose additional responsibility and liability in relation to the personal data that we process and we may be required to put in place additional mechanisms to ensure compliance with the new data protection rules. Additionally, the United Kingdom has implemented legislation, or the UK GDPR, that substantially implements the GDPR, with penalties for noncompliance of up to the greater of £17.5 million or four percent of worldwide revenues. Aspects of UK data protection laws and regulations remain unclear. On June 28, 2021, the European Commission announced a decision of "adequacy" concluding that the United Kingdom ensures an equivalent level of data protection to the GDPR, which provides some relief regarding the legality of continued personal data flows from the European Economic Area, or EEA, to the United Kingdom. Some uncertainty remains, however, as this adequacy determination must be renewed after four years and may be modified or revoked in the interim. We cannot fully predict how UK GDPR and data protection laws or regulations may develop in the medium-to-long term nor the effects of divergent laws and guidance regarding how data transfer to and from the United Kingdom will be regulated.

We may incur liabilities, expenses, costs, and other operational losses under the GDPR and the UK GDPR as well as privacy and data protection laws of Switzerland, the United Kingdom, and applicable EU Member States. We may find it necessary or appropriate to make additional changes to the ways we or our service providers collect, disclose, transfer, and otherwise process data within the EEA, Switzerland and the United Kingdom. This may be onerous and may interrupt or delay our development activities, and adversely affect our business, financial condition, results of operations and prospects.

Further, various states, such as California and Massachusetts, have implemented similar privacy laws and regulations that impose restrictive requirements regulating the use and disclosure of health information and other personally identifiable information. These laws and regulations are not necessarily preempted by the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, particularly if a state affords greater protection to individuals than HIPAA. Where state laws are more protective, we must comply with the stricter provisions. In addition to fines and penalties imposed upon violators, some of these state laws also afford private rights of action to individuals who believe their personal information has been misused. For example, California has recently enacted legislation, the California Privacy Rights Act, or CPRA, that, among other things, requires covered companies to provide new disclosures to California consumers, and affords such consumers new abilities to opt-out of certain sales of personal information. Some observers have noted the CPRA could be the beginning of a trend toward more stringent privacy legislation throughout the United States, as evidenced by privacy legislation recently enacted in Virginia, Colorado, Utah, and Connecticut. The CPRA requires covered companies to provide new disclosures to individuals and consumers in California, and afford such individuals and consumers new data protection rights, including the ability to opt-out of certain sales of personal information. The GDPR, UK GDPR, CPRA and many other federal, state, and foreign laws and regulations relating to privacy and data protection are still being tested in courts, and they are subject to new and differing interpretations by courts and regulatory officials. The U.S. federal government is also contemplating federal privacy legislation. Additionally, the interplay of federal and state laws may be subject to varying interpretations by courts and government agencies, creating complex compliance issues for us and data we receive, use and share, potentially exposing us to additional expense, adverse publicity and liability. We are working to comply with the GDPR, UK GDPR, CPRA and other privacy and data protection laws and regulations that apply to us, and we anticipate needing to devote significant additional resources to complying with these laws and regulations, as well as with the laws and regulations of any jurisdiction in which we may operate in the future. These and future laws and regulations may increase our compliance costs and potential liability.

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. See the section entitled “Business — Pharmaceutical Insurance Coverage and Healthcare Reform”.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for any of our product candidates that are approved for sale. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted 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.

Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain drug access and marketing cost disclosure and transparency measures, and designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, financial condition, results of operations and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our drugs or put pressure on our drug pricing, which could negatively affect our business, financial condition, results of operations and prospects.

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. 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. In particular, the implementation of any such cost containment measures may prevent us from being able to generate sufficient revenue, attain sustained profitability or commercialize KarXT for the treatment of schizophrenia, if approved, since we expect to derive the majority of future revenue from sales of KarXT in that indication from federal healthcare programs, including Medicare and Medicaid. Further, 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.

Any product candidates we develop may become subject to unfavorable third-party coverage and reimbursement practices, as well as pricing regulations.

Patients rely on insurance coverage by third-party payors (third-party payors include Medicare and Medicaid (government payors) and commercial insurance companies such as Blue Cross Blue Shield, Humana, Cigna, etc.) to reimburse all or part of the costs associated with their treatment. The availability and extent of coverage and adequate reimbursement by third-party payors, including government health administration authorities, private health coverage insurers, managed care organizations and other third-party payors is essential for most patients to be able to afford expensive treatments and is critical to new product acceptance. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the United States and internationally, on the extent to which the costs of such product candidates will be covered and reimbursed by third-party payors. No uniform policy exists for coverage and reimbursement in the United States. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize an adequate return on our investment. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not successfully commercialize any product candidate for which we obtain marketing approval. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. See the section entitled “Business — Pharmaceutical Insurance Coverage and Healthcare Reform”.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved products. In the United States, for example, principal decisions about reimbursement for new products 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. CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare, and private third-party payors often follow CMS’s decisions regarding coverage and reimbursement to a substantial degree. However, one third-party payor’s determination to provide coverage for a product candidate does not assure that other payors will also provide coverage for the product candidate. As a result, the coverage determination process is often time-consuming and costly. Factors payors consider in determining reimbursement are based on whether the product is: (i) a covered benefit under its health plan; (ii) safe, effective and medically necessary; (iii) appropriate for the specific patient; (iv) cost-effective; and (v) neither experimental nor investigational. This process will require us to provide scientific and clinical support for the use of our products to each third-party payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

As federal and state governments implement additional health care cost containment measures, including measures to lower prescription drug pricing, we cannot be sure that our products, if approved, will be covered by private or public payors, and if covered, whether the reimbursement will be adequate or competitive with other marketed products. For example, in July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. Further, the Biden administration released an additional executive order on October 14, 2022, directing HHS to submit a report within 90 days on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is unclear whether this executive order or similar policy initiatives will be implemented in the future. Such actions by federal and state governments and health plans may put additional downward pressure on pharmaceutical pricing and health care costs, which could negatively impact coverage and reimbursement for our products, if approved, our revenue, and our ability to compete with other marketed products and to recoup the costs of our research and development.

Additionally, net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs.

Outside the United States, the commercialization of therapeutics is generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the European Union, medical product prices are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after a product receives marketing approval. 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 candidate to other available therapies. In general, product prices under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

If we are unable to establish or sustain coverage and adequate reimbursement for any product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. 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 we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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 operate and plan to operate outside the United States, including those countries outside the United States in which we are conducting clinical trials as part of our EMERGENT, ARISE and ADEPT programs. 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.

Our operations in foreign jurisdictions, and those of our collaborators, may be impacted by economic, political and social conditions in such jurisdictions, as well as government policies, any of which could impact our ability to operate in such jurisdictions.

Our business is subject to risks associated with conducting business internationally. Some of our suppliers and collaborative relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, rising interest rates or political instability in certain non-U.S. economies and markets;
- differing and changing regulatory requirements in non-U.S. countries;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates and currency controls;

- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;
- negative consequences from changes in tax laws;
- potential liability under the FCPA, UK Bribery Act or comparable foreign laws;
- business interruptions resulting from geopolitical actions, including war, such as Russia's invasion of Ukraine, and terrorism, natural disasters including earthquakes, typhoons, floods and fires, or health epidemics such as COVID-19; and
- cyberattacks, which are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect.

For example, certain of the sites in our EMERGENT-3 Phase 3 clinical trial were located in Ukraine. As a result of Russia's invasion of Ukraine in February 2022, certain of these sites ceased recruiting and enrolling new patients in this trial earlier than expected, which delayed our anticipated topline data read-out from the second half of 2022 to the first quarter of 2023.

Additionally, through our license agreement with Zai Lab (Shanghai) Co., Ltd, or Zai, Zai has initiated clinical and regulatory activities in China. Accordingly, our business, results of operations, financial condition and prospects may be influenced to some degree by economic, political, legal and social conditions in China as well as China's economic, political, legal and social conditions in relation to the rest of the world.

Risks Related to Our Dependence on Third Parties

We have established a collaboration and may in the future seek to establish additional collaborations for the development and commercialization of our product candidates. If we are unable to enter into collaborations, 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. Additionally, there are certain jurisdictions where a collaborator may be able to realize the market potential of our product candidates better than us. For these or other reasons, 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. For example, in November 2021, we entered into a License Agreement, or the Zai License Agreement, with Zai, pursuant to which we granted to Zai the right to exclusively develop, manufacture and commercialize KarXT in Greater China, including mainland China, Hong Kong, Macau, and Taiwan.

If we choose to enter into additional collaborations, we will 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 our existing or any future collaboration is not successful, we may not be able to capitalize on the market potential of our product candidates.

The success of KarXT in Greater China depends on Zai's ability and efforts to successfully develop and commercialize KarXT in that territory. Additionally, we may enter into future collaborations for the development and commercialization of KarXT in other territories, or with respect to other product candidates we may license or develop. With respect to any such collaboration, 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. 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.

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.

While the Zai License Agreement contains provisions aimed to protect against many of these risks, including requirements that Zai diligently pursue the development and commercialization of KarXT in Greater China, and enabling us to reclaim the ability to develop and commercialize KarXT in China under certain circumstances, these provisions may prove insufficient. If our collaboration with Zai is not successful, our development and commercialization efforts in Greater China may be adversely affected.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any future collaboration is not successful, our business, financial condition, results of operations, prospects, and development and commercialization efforts may be adversely affected.

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, and we plan to do the same for KAR-2618. In particular, we rely and expect to continue to rely on a small number of manufacturers to supply us with our requirements for the API and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of API and formulated drugs. For example, supply chain issues resulting from the COVID-19 pandemic have resulted in limited availability of certain components of our drug formulation and may impact our ability to procure enough materials to support our ongoing and planned clinical trials as well as potential commercial manufacturing. Although we believe that there are several potential alternative manufacturers who could manufacture KarXT or supply such components in the event such issues persist or become more serious, we may incur added costs and delays in identifying and qualifying any such replacement.

In addition, we typically have ordered raw materials and services on a purchase order basis and do not usually 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 sufficient or adequate 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 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 ongoing 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.

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.

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 licensors 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. 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. 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.

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.

We, or any future partners, collaborators, or licensees, may also 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.

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, 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.

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. 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, 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.

The patent position of biotechnology and pharmaceutical companies carries risks and uncertainties, any of which could have a material adverse effect on our ability to generate revenue. These risks and uncertainties include the following:

- 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;
- patent applications may not result in any patents being issued;
- if we fail to comply with the procedural, documentary, fee payment and other requirements of the USPTO or the various foreign governmental patent agencies during the patent process, it could result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction;
- 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;
- patents have a limited lifespan, and patents protecting our product candidates might expire before or shortly after such candidates are commercialized, which could allow others to commercialize products similar to our product candidates;
- 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;
- 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; and
- changes to either the patent laws or interpretation of the patent laws in the United States and other countries could diminish the value of our patents or narrow the scope of our patent protection.

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.

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 license agreements with PureTech Health and the assignment estate of Goldfinch Bio, Inc., or GFB, that provide us with intellectual property rights relating to KarXT and KAR-2618, respectively. These license agreements impose milestone payment, royalty and other obligations on us. If we fail to comply with our obligations, including achieving specified milestone events, PureTech Health and GFB may have the right to terminate their respective license agreement, 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 or GFB, as applicable, 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 candidates, 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 us, our licensors 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.

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. 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 five 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 could increase those uncertainties and costs. For example, the Leahy-Smith America Invents Act, or the America Invents Act, reformed 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. 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, including India, China, and other developing 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. 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. 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.

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 and retain the services of our current executive officers, principal consultants and others, including William Meury, our President and Chief Executive Officer, Andrew Miller, our Chief Operating Officer, Steven Paul, our Chief Scientific Officer and President of Research and Development, Stephen Brannan, our Chief Medical Officer, Troy Ignelzi, our Chief Financial Officer, and William Kane, our Chief Commercial Officer. We have entered into employment agreements with Mr. Meury, Dr. Paul, Dr. Miller, Dr. Brannan, Mr. Ignelzi and Mr. Kane, 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, medical and commercial 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.

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;
- insider trading laws;
- 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 continue 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, 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 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

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, KAR-2618 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.

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, 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 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 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting and include with this annual report an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To comply with Section 404, 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 34,515,033 shares outstanding as of February 15, 2023, 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 42.4% of our common stock. If our stockholders who own more than 5% of our outstanding common stock were to choose to act together, they may have significant influence over 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, may have significant influence over 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.

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.

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, 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. If this were to occur, we could also be subject to sanctions or investigations by the SEC or other regulatory authorities.

We are required to disclose material 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, 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.

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 bylaws contain exclusive forum provisions, which may limit a stockholder's ability to bring a claim in a judicial forum it finds favorable and may discourage lawsuits with respect to such claims.

Our amended and restated bylaws, or bylaws, provide that unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for state law claims for (1) any derivative action, (2) any claim of breach of fiduciary duty, (3) any claim against a current or former director, officer, employee or stockholder, and (4) any action against our company governed by the internal affairs doctrine, which we refer to collectively as the Delaware forum provision. The Delaware forum provision does not apply to any claims arising under the Securities Exchange Act of 1934 or the Securities Act of 1933, as amended, or the Securities Act. Our bylaws further provide that, unless we consent in writing to an alternative forum, the federal district courts of the United States of America shall be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act, which we refer to as the federal forum provision. In addition, our bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the Delaware forum provision and the federal forum provision.

We believe that these exclusive forum provisions benefit 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, these provisions may impose additional litigation costs on stockholders who assert the provisions are not enforceable or valid and may impose more general additional litigation costs in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware. In addition, these forum selection clauses in our bylaws may limit our stockholders' ability to bring a claim in a judicial forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. Alternatively, if the federal forum provision is found inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have an adverse effect on our business, financial condition or results of operations. The Court of Chancery of the State of Delaware and the federal district courts of the United States of America may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

General Risks

Our business may be adversely affected by a pandemic, epidemic or outbreak of an infectious disease, such as the ongoing COVID-19 pandemic and the emergence of additional variants.

Health epidemics could adversely affect our business in regions where we have concentrations of clinical trial sites or other business activities and could cause significant disruption in the operations of third-party contract manufacturers and contract research organizations upon whom we rely, as well as our ability to recruit patients for our clinical trials. For example, the ongoing COVID-19 pandemic continues to have unpredictable impacts on global societies, economies, financial markets, and business practices around the world.

The extent to which the ongoing COVID-19 pandemic may impact our business, results of operations and future growth prospects will depend on a variety of factors and future developments, which are highly uncertain and cannot be predicted with confidence, including the duration, scope and severity of the pandemic, particularly as virus variants continue to spread. For example, we experienced, and may experience again, some temporary delays or disruptions due to the COVID-19 pandemic, including pauses in and delays to patient dosing, limited or reduced patient access to ICU beds, hospitals and healthcare resources generally, delayed initiation of new clinical trial sites and limited on-site personnel support at various trial sites. In addition, 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. We currently rely and expect to continue to rely on a small number of manufacturers to provide the APIs of KarXT and for the final drug product formulation of KarXT that is being used in our clinical trials. These programs could be adversely affected by ongoing supply chain issues caused by the COVID-19 pandemic.

We are actively monitoring and managing our response and evaluating the actual and potential impacts to our business operations, including on our ongoing and planned clinical trials. We will continue to work closely with our third-party vendors, collaborators, and other parties in order to seek to advance our programs and pipeline of product candidates, while keeping the health and safety of our employees and their families, partners, third-party vendors, healthcare providers, patients and communities a top priority.

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, prevent new or modified products from being developed, approved, or commercialized in a timely manner or at all, or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, 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 on which our operations rely, such as the SEC and those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs or modifications to approved drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in 2018 and 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities.

Since March 2020 when foreign and domestic inspections of facilities were largely placed on hold in response to the COVID-19 pandemic, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. While the FDA has largely caught up with domestic preapproval inspections, it continues to work through its backlog of foreign inspections. In addition, regulatory authorities outside the United States 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.

Further, in our operations as a public company, future government shutdowns or other disruptions to normal operations could impact our ability to access the public markets and obtain the funding necessary to properly capitalize and continue our operations.

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. In addition, a majority of our employees are working remotely. As a result, we may have increased susceptibility to cyber security and data security risks due to increased use of home wi-fi networks and virtual private networks, as well as increased disbursement of physical machines. While we implement IT controls to reduce the risk of a cyber security or data security breach, 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.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our headquarters are located at 99 High Street, 26th Floor, Boston, Massachusetts, where we occupied approximately 25,445 square feet of leased office space as of December 31, 2022. This lease expires in December 2025.

We also lease approximately 11,225 square feet of office space at 33 Arch Street, Suites 3110, 3130 and 3150, Boston Massachusetts. This lease expires in December 2023. As of December 31, 2022, the entirety of this office space is subleased to third parties.

Additionally, we occupy 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.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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, 2023, there were approximately 4 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

None.

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 primarily built on the broad therapeutic potential of our lead product candidate, KarXT (xanomeline-trospium), 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.

We have never generated revenue from product sales and have incurred significant net losses since inception. Our net losses were $276.3 million, $143.8 million and $68.6 million for the years ended December 31, 2022, 2021, and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $564.2 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, including KAR-2618 (formerly GFB-887), 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 may 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, 2022, we had cash, cash equivalents and available-for-sale investments of $1,124.0 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 through the end of 2025. 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 from product sales. 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. 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.

Our revenue to date has been derived from payments under our license agreement, or the Zai License Agreement, with Zai Lab (Shanghai) Co., Ltd., or Zai. We may also generate revenue in the future from payments under the Zai License Agreement or as a result of license or collaboration agreements for any of our product candidates or intellectual property. For the years ended December 31, 2022 and 2021, we recognized revenue of $10.6 million and $37.0 million, respectively, under the Zai License Agreement. We cannot provide assurance as to the timing of future milestone or royalty payments under the Zai License Agreement, or that we will receive any of these payments at all. We generated no revenue from license or collaboration agreements in the year ended December 31, 2020.

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.

Research and development costs directly related to our clinical development activities, such as fees paid to consultants, central laboratories, contractors, CMOs and CROs are tracked on an indication-by-indication basis. Other costs that are indirectly related to our clinical development activities, such as formulation and CMC, preclinical, discovery and unallocated expenses in the table below 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. Unallocated expenses primarily relate to personnel or other consulting costs which are deployed across multiple projects under development. The following table summarizes our research and development expenses:

	Year Ended December 31,		
	2022	2021	2020
Schizophrenia clinical trials	$ 103,474	$ 62,167	$ 11,803
Dementia-related psychosis clinical trials	7,531	1,573	1,465
Pain clinical trial	-	143	1,297
CMC and formulation	28,175	15,943	8,987
Preclinical	2,086	2,469	898
Discovery	19,006	14,068	5,555
Unallocated expenses	63,975	31,837	13,403
Total research and development expense	$ 224,247	$ 128,200	$ 43,408

We expect our research and development expenses to continue to increase 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, including KAR-2618;
- 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;
- continue to 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 may 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, short-term incentive compensation, 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, Net

Other income, net, consists of interest income from our cash equivalents and available-for-sale investments and sublease income recognized in connection with the sublease of office space, offset by impairment loss on our right-of-use lease assets at our Arch Street facility, due to their carrying value exceeding their estimated fair value.

Income Taxes

We recorded income tax expense of $1.4 million during the year ended December 31, 2022 primarily due to revenue recognized in connection with the Zai License Agreement. 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, 2022, 2021 and 2020 as we believed, based upon the weight of available evidence, that it was more likely than not that all of our net operating loss carryforwards and tax credits will not be realized. At December 31, 2022, we had federal net operating loss carryforwards totaling $406.5 million, of which $9.8 million begin to expire in 2029 and $396.7 million can be carried forward indefinitely. At December 31, 2022, we had state net operating loss carryforwards totaling $321.5 million which begin to expire in 2030. The federal and state operating loss carryforwards may be available to offset future income tax liabilities. Because we had historically been a subsidiary of PureTech Health, $406.0 million and $301.5 million of the federal and state net operating loss carryforwards, respectively, can be used to offset income on our future tax returns. As of December 31, 2022, we also had federal and state research and development tax credit carryforwards of $34.9 million and $4.9 million, respectively, which begin to expire in 2031. Through December 31, 2022, we had recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

	Year Ended December 31,		
	2022	2021	Change
		(in thousands)	
License and other revenue	$ 10,637	$ 36,964	$ (26,327)
Operating expenses:			
Research and development	224,247	128,200	96,047
General and administrative	76,066	52,617	23,449
Total operating expenses	300,313	180,817	119,496
Loss from operations	(289,676)	(143,853)	(145,823)
Total other income, net	14,758	54	14,704
Income tax provision	(1,418)	(6)	(1,412)
Net loss attributable to common stockholders	$ (276,336)	$ (143,805)	$ (132,531)

Research and Development Expenses

	Year Ended December 31,		
	2022	2021	Change
		(in thousands)	
Direct research and development expenses:			
Schizophrenia clinical trials	$ 103,474	$ 62,167	$ 41,307
Dementia-related psychosis clinical trials	7,531	1,573	5,958
Pain clinical trial	-	143	(143)
CMC and formulation	28,175	15,943	12,232
Preclinical	2,086	2,469	(383)
Discovery	19,006	14,068	4,938
Unallocated expenses:			
Personnel related (including stock-based compensation)	53,883	29,524	24,359
Consultant fees and other expenses	10,092	2,313	7,779
Total research and development expense	$ 224,247	$ 128,200	$ 96,047

Expenses related to our schizophrenia clinical trials increased by $41.3 million, primarily due to expenses related to enrollment and close out costs related to our EMERGENT Phase 3 trials, and enrollment related to our ARISE Phase 3 trials. The increase of $6.0 million in expenses related to our DRP clinical trial is primarily driven by start-up costs for, and initiation of, the ADEPT-1 Phase 3 trial in the third quarter of 2022. The decrease of $0.1 million in expenses related to our pain clinical trial is due to unrepeated costs of closing out the Phase 1b trial in 2021. Formulation and CMC expenses increased by $12.2 million due to an increase in manufacturing activities in 2022 to obtain sufficient supply of KarXT to support current and future clinical trial activities as well as activities to support a planned NDA submission and potential commercialization. The decrease of $0.4 million in expenses related to preclinical activities is primarily due to the timing and execution of studies in 2022. The increase of $4.9 million in discovery costs is due to an increase in costs associated with our portfolio of discovery programs, including ongoing collaborations with Charles River Labs and Psychogenics, Inc. The increase of $24.4 million in personnel related costs was primarily a result of an increase in headcount and an increase of $9.3 million related to stock-based compensation expense. The increase of $7.8 million in consultant fees and other expenses was due to timing of consulting costs not specifically allocated to discovery, preclinical, clinical, formulation or CMC activities.

General and Administrative Expenses

	Year Ended December 31,		
	2022	2021	Change
		(in thousands)	
Personnel-related (including stock-based compensation)	$ 44,677	$ 27,409	$ 17,268
Professional and consultant fees	19,388	12,674	6,714
Other	12,001	12,534	(533)
Total general and administrative expense	$ 76,066	$ 52,617	$ 23,449

The increase of $17.3 million in personnel related costs was primarily a result of an increase in headcount and an increase of $8.3 million related to stock-based compensation expense. The increase of $6.7 million in professional and consultant fees was primarily due to an increase in recruiting fees, accounting fees, pre-commercial costs, legal costs and consulting fees related to our ongoing business activities. The decrease of $0.5 million in other expenses was primarily due to foreign tax withholdings on upfront payments received from Zai under the Zai License Agreement, offset by increased lease costs relating to the addition of the High Street Lease in Boston, Massachusetts in March 2021 as well as other infrastructure and administrative related costs to support increased headcount.

Other Income, Net

	Year Ended December 31,		
	2022	2021	Change
		(in thousands)	
Interest income	$ 14,178	$ 502	$ 13,676
Sublease income	580	254	326
Impairment loss on right-of-use assets	—	(702)	702
Total other income, net	$ 14,758	$ 54	$ 14,704

Interest income is attributable to interest earned on our cash equivalents and available-for-sale investments. The increase of $13.7 million in interest income is primarily due to an increase in cash equivalents and investment securities held, as well as an increase in interest rates on such instruments for the year ended December 31, 2022 compared to December 31, 2021.

The increase in sublease income is due to the sublease of our Arch Street office space in Boston, Massachusetts, a portion of which commenced in June 2021. As of January 21, 2022, all leases at at our Arch

Street office space in Boston, Massachusetts have been subleased through the end of their lease terms, which end on December 31, 2023.

Impairment loss on right-of-use assets for the year ended December 31, 2021 represents impairment recognized on our right-of-use lease assets to the extent their carrying value exceeded their estimated fair value for our Arch Street facility leases in Boston, Massachusetts. See Note 10 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Comparison of the Years Ended December 31, 2021 and 2020

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
License and other revenue	$ 36,964	$ —	$ 36,964
Operating expenses:			
Research and development	128,200	43,408	84,792
General and administrative	52,617	28,408	24,209
Total operating expenses	180,817	71,816	109,001
Loss from operations	(143,853)	(71,816)	(72,037)
Total other income, net	54	3,305	(3,251)
Income tax provision	(6)	(43)	37
Net loss attributable to common stockholders	$ (143,805)	$ (68,554)	$ (75,251)

Research and Development Expenses

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Direct research and development expenses:			
Schizophrenia clinical trials	$ 62,167	$ 11,803	$ 50,364
Dementia-related psychosis clinical trials	1,573	1,465	108
Pain clinical trial	$ 143	$ 1,297	$ (1,154)
CMC and formulation	15,943	8,987	6,956
Preclinical	2,469	898	1,571
Discovery	14,068	5,555	8,513
Unallocated expenses:			
Personnel related (including stock-based compensation)	29,524	11,134	18,390
Consultant fees and other expenses	2,313	2,269	44
Total research and development expense	$ 128,200	$ 43,408	$ 84,792

Expenses related to our schizophrenia clinical trials increased by $50.4 million, primarily due to expenses related to startup and ongoing execution of our EMERGENT and ARISE Phase 3 trials. The increase of $0.1 million in expenses related to our DRP clinical trial is primarily driven by enrollment, dosing and close-out activities related to our completed Phase 1b clinical trial in healthy elderly volunteers. The decrease of $1.2 million in expenses related to our pain clinical trial is primarily due to unrepeated costs for enrollment and dosing activities incurred in 2020 for our Phase 1b trial compared to close out costs for that trial incurred in 2021. Formulation and CMC expenses increased by $7.0 million due to an increase in manufacturing activities in 2021 to obtain sufficient supply to support current and future clinical trial activities as well as activities to support a potential future NDA filing. Preclinical expenses increased by $1.6 million due to the initiation of new studies in late 2020 and into 2021. The increase of $8.5 million in discovery costs is due to an increase in efforts for future product candidates, including ongoing collaborations with Charles River Labs and Psychogenics, Inc. The increase of $18.4 million in personnel related costs was primarily a result of an increase in headcount and an increase of $7.9 million related to stock-based compensation expense. The

decrease of less than $0.1 million in consultant fees and other expenses was due to timing of consulting costs not specifically allocated to discovery, preclinical, clinical, formulation or CMC activities.

General and Administrative Expenses

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Personnel-related (including stock-based compensation)	$ 27,409	$ 16,701	$ 10,708
Professional and consultant fees	12,674	5,162	7,512
Other	12,534	6,545	5,989
Total general and administrative expense	$ 52,617	$ 28,408	$ 24,209

The increase of $10.7 million in personnel related costs was primarily a result of an increase in headcount and an increase of $8.5 million related to stock-based compensation expense. The increase of $7.5 million in professional and consultant fees was primarily due to an increase in recruiting fees, accounting fees, pre-commercial costs, legal costs and consulting fees related to our ongoing business activities. The increase of $6.0 million in other expenses was primarily due to $3.7 million in foreign tax withholdings on upfront payments received from Zai under the Zai License Agreement, increased lease costs due to our High Street Lease in Boston, Massachusetts, as well as other infrastructure and administrative related costs to support increased headcount.

Other Income, Net

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Interest income	$ 502	$ 3,305	$ (2,803)
Sublease income	254	—	254
Impairment loss on right-of-use assets	(702)	—	(702)
Total other income, net	$ 54	$ 3,305	$ (3,251)

Interest income is attributable to interest earned on our cash equivalents and available-for-sale investments. The decrease of $2.8 million in interest income is primarily due to lower market interest rates.

Sublease income is due to the sublease of a portion of our Arch Street office space in Boston, Massachusetts during 2021.

Impairment loss on right-of-use assets for the year ended represents impairment recognized on our right-of-use lease assets to the extent their carrying value exceeded their estimated fair value for our Arch Street facility leases in Boston, Massachusetts. See Note 10 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

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 until we receive FDA approval, which we expect will take a number of years, if ever. To date, we have funded our operations primarily with proceeds from the sale of redeemable convertible preferred stock, issuance of convertible notes, sales of our common stock and revenue from a license agreement. Through December 31, 2022, our operations have been financed by 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 in June 2019, $234.2 million from the sale of our common stock in a follow-on public offering in November 2019, $270.0 million from the sale of our common stock in a follow-on public offering in March 2021, $819.1 million from the sale of our common stock in a follow-on public offering in August 2022, and $45.0 million from the Zai License Agreement. As of December 31, 2022, we had $1,124.0 million in cash, cash equivalents and available-for-sale investments, and an accumulated deficit of $564.2 million.

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. We may sell common stock pursuant to the equity distribution agreement from time to time in varying amounts, which may be limited, based upon factors including (among others) market conditions, investor demand, the trading price of our common stock, and determinations by us of our need for, and appropriate sources of, additional capital. As of December 31, 2022, 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 prepaid expenses, 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,		
	2022	2021	2020
		(in thousands)	
Net cash used in operating activities	$ (228,006)	$ (100,878)	$ (69,856)
Net cash used in investing activities	(586,395)	(22,688)	(89,650)
Net cash provided by financing activities	855,777	277,575	3,659
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 41,376	$ 154,009	$ (155,847)

Cash Flows from Operating Activities

Cash used in operating activities for the year ended December 31, 2022 was $228.0 million, consisting of a net loss of $276.3 million adjusted for noncash items, including stock-based compensation of $47.5 million, and interest income resulting from the amortization of premiums and accretion of discounts on our available-for-sale investments of $5.0 million. The change in our net operating assets and liabilities was primarily due to a decrease in accounts receivable of $1.7 million related to payments received under the Zai License Agreement, and increases in prepaid expenses of $9.0 million and accrued expenses of $13.2 million, primarily driven by timing of payments made to and services rendered by CROs and CMOs in connection with our clinical trials, as well as an increase in personnel related accruals due to increased headcount.

Cash used in operating activities for the year ended December 31, 2021 was $100.9 million, consisting of a net loss of $143.8 million adjusted for noncash items, including stock-based compensation of $29.8 million, interest expense resulting from the amortization of premiums and accretion of discounts on our available-for-sale investments of $1.1 million, and impairment loss on right-of-use assets of $0.7 million. The change in our net operating assets and liabilities was primarily due to an increase in accrued expenses of $10.9 million, mainly driven by expenses incurred and timing of payments to CROs and CMOs in connection with and in support of our clinical trial activities, as well as an increase personnel related accruals due to increased headcount.

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 amortization of premiums and accretion of discounts on available-for-sale investments 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 Flows from Investing Activities

Cash used in investing activities for the year ended December 31, 2022 was $586.4 million, consisting primarily of $930.3 million for the purchases of investment securities, partially offset by maturities of investment securities of $344.8 million.

Cash used in investing activities for the year ended December 31, 2021 was $22.7 million, consisting primarily of $400.8 million for the purchases of investment securities and $3.1 million for the acquisition of property and equipment, partially offset by maturities and sales of investment securities of $372.2 million and $9.0 million, respectively.

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 Flows from Financing Activities

Cash provided by financing activities for the year ended December 31, 2022 was $855.8 million and was attributable to $818.9 million in net proceeds received from the sale of our common stock in our follow-on public offering and $36.8 million attributable to proceeds received from the exercise of stock options.

Cash provided by financing activities for the year ended December 31, 2021 was $277.6 million and was attributable to $270.0 million in net proceeds received from the sale of our common stock in our follow-on public offering and $7.6 million attributable to proceeds received from the exercise of stock options.

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.

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, 2022, we had cash, cash equivalents and available-for-sale investments of $1,124.0 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 through the end of 2025.

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, including KAR-2618;
- 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 the receipt of regulatory approval, the revenue received, if any, 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 and 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.

Cash Requirements due to Contractual Obligations and Other Commitments

We are currently under agreements to lease our Arch Street office space through December 2023. Remaining lease payments from January 1, 2023 through the end of the lease term total $0.9 million. As of January 21, 2022, all leases at at our Arch Street office space in Boston, Massachusetts have been subleased through the end of their lease terms.

We are also under agreement to lease office space in Carmel, Indiana through July 2023. Remaining lease payments total less than $0.1 million through the end of the lease term.

In March 2021, we entered into an agreement to sublease approximately 25,445 square feet of office space, or the High Street Premises, from a third party in Boston, Massachusetts as part of the relocation of our corporate headquarters. The term of the sublease extends from April 1, 2021 through December 31, 2025 and provides for escalating annualized base rent payments starting at approximately $1.5 million and increasing to $1.6 million in the final year of the sublease. Remaining lease payments from January 1, 2023 through the end of the lease term total $4.8 million.

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 generally cancelable by us upon prior written notice. Payments due upon cancellation consist of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation, and may also include termination penalties. As of December 31, 2022 the timing, amount or likelihood 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 may be obligated to make 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. As of December 31, 2022, 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 prepaid and 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 prepaid expenses and other current assets and accrued expenses in the balance sheets and within research and development expense in the statements of operations. When evaluating the future utility of the prepaid expenses and adequacy of the accrued expenses, 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 prepaid and accrual estimates have not been materially different from the actual costs.

Recently Issued and Adopted Accounting Pronouncements

A description of recently issued accounting pronouncements that have been recently adopted or 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 $1,124.0 million as of December 31, 2022, which consisted primarily of money market funds and investment securities, largely composed of U.S. Treasuries and Agencies 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. We intend and have the ability to hold those investments to maturity and, should interest rates rise, there would be no recognition of impairment required. Declines in interest rates, however, could reduce future investment income. 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.

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, 2022, 2021 and 2020. However, inflation has had, and may continue to have, an impact on the labor costs we incur to attract and retain qualified personnel.

ITEM 8. CONSOLIDATED FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2022, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2022, 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, 2022 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, 2022, prepaid research and development expenses totaled $25.3 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, 2022 and evaluating whether services received prior to December 31, 2022 were included in the Company's estimate of costs incurred as of December 31, 2022.

/s/ KPMG LLP

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

Boston, Massachusetts
February 23, 2023

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

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 248,329	$ 206,953
Investment securities, available-for-sale	875,715	287,038
Accounts receivable	57	1,750
Prepaid expenses and other current assets	30,100	21,138
Deferred offering costs	568	455
Total current assets	1,154,769	517,334
Restricted cash	261	261
Right-of-use lease assets - operating, net	4,674	6,453
Property and equipment, net	3,201	3,092
Other non-current assets	429	531
Total assets	$ 1,163,334	$ 527,671
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,379	$ 1,939
Accrued expenses	29,285	16,099
Current portion of operating lease liability	2,282	2,175
Total current liabilities	33,946	20,213
Operating lease liability, net of current portion	3,046	5,328
Other non-current liabilities	104	104
Total liabilities	37,096	25,645
Commitments and Contingencies (Note 10)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized and 0 shares outstanding at December 31, 2022 and 2021	—	—
Common stock, $0.0001 par value; 150,000,000 shares authorized at December 31, 2022 and 2021; 34,473,905 and 29,770,558 shares issued and outstanding at December 31, 2022 and 2021, respectively	3	3
Additional paid-in capital	1,693,732	790,391
Accumulated deficit	(564,207)	(287,871)
Accumulated other comprehensive loss	(3,290)	(497)
Total stockholders' equity	1,126,238	502,026
Total liabilities and stockholders' equity	$ 1,163,334	$ 527,671

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,		
	2022	**2021**	**2020**
License and other revenue	$ 10,637	$ 36,964	$ —
Operating expenses:			
Research and development	224,247	128,200	43,408
General and administrative	76,066	52,617	28,408
Total operating expenses	300,313	180,817	71,816
Loss from operations	(289,676)	(143,853)	(71,816)
Other income, net:			
Interest income	14,178	502	3,305
Sublease income	580	254	—
Impairment loss on right-of-use assets	-	(702)	—
Total other income, net	14,758	54	3,305
Net loss before income taxes	(274,918)	(143,799)	(68,511)
Income tax provision	(1,418)	(6)	(43)
Net loss attributable to common stockholders	$ (276,336)	$ (143,805)	$ (68,554)
Net loss per share, basic and diluted (Note 7)	$ (8.74)	$ (4.94)	$ (2.59)
Weighted average common shares outstanding used in computing net loss per share, basic and diluted	31,629,013	29,138,915	26,446,006

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,		
	2022	**2021**	**2020**
Net loss	$ (276,336)	$ (143,805)	$ (68,554)
Other comprehensive (loss) income:			
Unrealized (losses) gains on available-for-sale investments	(2,793)	(536)	34
Comprehensive loss	$ (279,129)	$ (144,341)	$ (68,520)

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

KARUNA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(In thousands, except share data)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Value				
Balance, December 31, 2019	26,012,754	$ 3	$ 465,420	$ (75,512)	$ 5	$ 389,916
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
Issuance of common stock upon public offering, net of $17,250 in under-writing discounts and commissions and $233 in offering costs	2,395,834	—	270,017	—	—	270,017
Stock-based compensation expense	—	—	29,811	—	—	29,811
Exercise of common options	386,266	—	7,608	—	—	7,608
Other comprehensive loss	—	—	—	—	(536)	(536)
Net loss	—	—	—	(143,805)	—	(143,805)
Balance, December 31, 2021	29,770,558	$ 3	$ 790,391	$ (287,871)	$ (497)	$ 502,026
Issuance of common stock upon public offering, net of $43,125 in under-writing discounts and commissions and $328 in offering costs	4,011,628	—	819,047	—	—	819,047
Stock-based compensation expense	—	—	47,451	—	—	47,451
Exercise of common options	691,719	—	36,843	—	—	36,843
Other comprehensive loss	—	—	—	—	(2,793)	(2,793)
Net loss	—	—	—	(276,336)	—	(276,336)
Balance, December 31, 2022	34,473,905	$ 3	$ 1,693,732	$ (564,207)	$ (3,290)	$ 1,126,238

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,		
	2022	**2021**	**2020**
Cash flows from operating activities			
Net loss	$ (276,336)	$ (143,805)	$ (68,554)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	47,451	29,811	13,471
Impairment loss on right-of-use assets	—	702	—
Amortization of premiums and accretion of discounts on investment securities	(5,007)	1,063	642
Depreciation and amortization expense	1,112	506	145
Loss on disposal of assets	—	—	20
Changes in operating assets and liabilities:			
Accrued interest on investment securities	(983)	261	(191)
Accounts receivable	1,693	(1,750)	—
Prepaid expenses and other current assets	(8,962)	726	(18,555)
Right-of-use assets	1,779	1,305	631
Other non-current assets	102	(531)	—
Accounts payable	243	1,071	318
Accrued expenses	13,077	10,881	2,791
Operating lease liability	(2,175)	(1,222)	(574)
Other non-current liabilities	—	104	—
Net cash used in operating activities	(228,006)	(100,878)	(69,856)
Cash flows from investing activities			
Purchases of investment securities	(930,280)	(400,829)	(344,213)
Maturities of investment securities	344,800	372,223	254,982
Sales of investment securities	—	8,990	—
Acquisition of property and equipment	(915)	(3,072)	(419)
Net cash used in investing activities	(586,395)	(22,688)	(89,650)
Cash flows from financing activities			
Proceeds from public offering, net of underwriting discounts and commissions	819,375	270,250	—
Payment of offering costs	(441)	(283)	(439)
Proceeds from exercise of stock options	36,843	7,608	4,098
Net cash provided by financing activities	855,777	277,575	3,659
Net increase (decrease) in cash, cash equivalents and restricted cash	41,376	154,009	(155,847)
Cash, cash equivalents and restricted cash at beginning of period	207,214	53,205	209,052
Cash, cash equivalents and restricted cash at end of period	$ 248,590	$ 207,214	$ 53,205
Supplemental disclosures of cash flows information			
Purchases of property and equipment included in accounts payable and accrued expenses	$ 306	$ 77	$ —
Lease liabilities arising from obtaining right-of-use assets	$ —	$ 6,040	$ 3,259

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

NOTES TO 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 ongoing and evolving COVID-19 coronavirus pandemic, and the need to obtain adequate additional financing to fund the development of its product candidates.

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, 2022, no sales had been made pursuant to the ATM Program.

On March 4, 2021, the Company completed a follow-on public offering under the Registration Statement and a related prospectus supplement in which it issued and sold 2,395,834 shares of common stock, including full exercise of the underwriters' over-allotment option to purchase an additional 312,500 shares of common stock, at a public offering price of $120 per share. The aggregate net proceeds to the Company from the offering, inclusive of proceeds from the over-allotment exercise, were $270.0 million after deducting underwriting discounts and commissions of $17.3 million and offering expenses of $0.2 million.

On August 9, 2022, the Company completed a follow-on public offering under the Registration Statement and a related prospectus supplement in which it issued and sold 4,011,628 shares of common stock, including full exercise of the underwriters' over-allotment option to purchase an additional 523,255 shares of common stock, at a public offering price of $215 per share. The aggregate net proceeds to the Company from the offering, inclusive of proceeds from the over-allotment exercise, were $819.1 million after deducting underwriting discounts and commissions of $43.1 million and offering expenses of $0.3 million.

The Company's consolidated 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 $228.0 million for the year ended December 31, 2022 and had an accumulated deficit of $564.2 million as of December 31, 2022. 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 $1,124.0 million as of December 31, 2022 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.

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

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, revenue and the accrual of research and development expenses. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company's estimates.

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 (loss) income 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, 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 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 associated with the Company's ATM Program were $0.6 million and $0.5 million as of December 31, 2022 and 2021, respectively. All other deferred offering costs accumulated during the years ended December 31, 2022 and 2021 and associated with the Company's public offerings were recorded as a reduction of additional paid-in capital upon the close of the Company's public offerings on August 9, 2022 and March 4, 2021, respectively.

Fair Value of Financial Instruments

The Company's financial instruments consist of cash equivalents, investment securities, accounts receivable, prepaid expenses and other current assets, accounts payable, and accrued expenses. The carrying amount of accounts receivable, prepaid expenses and other current assets, accounts payable, and accrued expenses are considered a reasonable estimate of their fair value, due to the short-term maturity of these instruments. The Company's cash equivalents and investment securities are carried at fair value, determined according to the fair value hierarchy described below (see Note 9).

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.

Impairment of Long-Lived Assets

The Company continually evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the carrying values of the assets to the expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book values of the assets exceed their fair value.

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.

At the inception of an arrangement, the Company determines 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. The Company does 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, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company 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 the Company's incremental borrowing rate, a credit rating applicable to the Company is estimated using a synthetic credit rating analysis since the Company does not currently have a rating agency-based credit rating. Prospectively, the Company 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.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that it will renew.

Assumptions that the Company 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.

Sublease income is recognized on a straight-line basis over the term of the sublease agreement and is recorded within other income, net, on the consolidated statements of operations.

Revenue

The Company recognizes revenue in accordance with FASB ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and, if so, they are considered performance obligations. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether they are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct in the context of a collaboration or licensing arrangement, the Company considers factors such as the research, manufacturing and commercialization capabilities of a collaboration partner and the availability of the associated expertise in the general marketplace (see discussion of license agreement in Note 8). The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their stand-alone selling prices ("SSP") on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is limited to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. If over time, recognition is based on the use of either an output or an input method, such that the method used best depicts the transfer of control to the customer.

Amounts received from a customer prior to revenue recognition are recorded as deferred revenue. Amounts received from a customer that are expected to be recognized as revenue within the 12 months following the balance sheet date are classified as a current liability in the accompanying consolidated balance sheets.

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 expenses (or prepaid expenses, as appropriate) in the balance sheets and within research and development expense in the statements of operations. When evaluating the future utility of prepaid expenses and the adequacy of accrued expenses, 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 prepaid or accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical prepaid and 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.

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

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 attributable to common stockholders is computed by adjusting income attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities, including outstanding stock options. Diluted net income per share attributable to common stockholders is computed by dividing the diluted net income 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.

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, 2022, 2021 and 2020.

Comprehensive Loss

Comprehensive (loss) income includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2022, 2021 and 2020, the Company's only element of other comprehensive loss was unrealized (losses) gains on available-for-sale investments.

Recently Issued Accounting Pronouncements

New pronouncements issued but not effective until after December 31, 2022 are not expected to 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,	
	2022	2021
Leasehold improvements	$ 1,367	$ 1,351
Furniture and fixtures	1,020	984
Computer equipment	999	575
Office equipment	673	487
Software	596	267
Assets not yet in service	226	—
Total property and equipment	4,881	3,664
Less: accumulated depreciation	(1,680)	(572)
Property and equipment, net	$ 3,201	$ 3,092

Depreciation expense was $1.1 million for the year ended December 31, 2022, $0.5 million for the year ended December 31, 2021, and $0.1 million for the year ended December 31, 2020.

Note 4. Prepaid Expenses and Other Assets and Accrued Expenses

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

	December 31,	
	2022	2021
Research and development expenses	$ 25,285	$ 18,066
Insurance	2,472	2,364
Other	2,343	708
Total prepaid expenses and other current assets	$ 30,100	$ 21,138

The Company also had other non-current assets of $0.4 million as of December 31, 2022, which consisted of a security deposit of $0.4 million and less than $0.1 million in prepaid expenses.

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2022	2021
Research and development expenses	$ 11,962	8,316
Payroll and related expenses	11,950	$ 6,989
Professional fees	2,943	543
Other	2,430	251
Total accrued expenses	$ 29,285	$ 16,099

Note 5. Stockholders' Equity

Preferred Stock

On July 2, 2019, in connection with the closing of the Company's IPO, the Company filed its amended and 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. Through December 31, 2022, no preferred stock has been issued.

Common Stock

As of December 31, 2022, the Company's amended and restated 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 are 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, 2022, no cash dividends have been declared or paid.

As of December 31, 2022, there were 34,473,905 shares of common stock outstanding.

Note 6. Zai License Agreement

Terms of Agreement

On November 8, 2021, the Company and Zai Lab (Shanghai) Co., Ltd. ("Zai") entered into a license agreement (the "Zai License Agreement"), pursuant to which Karuna granted to Zai the right to exclusively develop, manufacture and commercialize KarXT in Greater China, including mainland China, Hong Kong, Macau, and Taiwan (the “Licensed Territory”). Zai will fund substantially all development, regulatory, and commercialization activities in the Licensed Territory.

Under the terms of the Zai License Agreement, the Company received a non-refundable $35.0 million upfront payment and payment of certain taxes on its behalf. The Zai License Agreement also provides that the Company is eligible to receive total development and regulatory milestone payments of up to $80.0 million, total sales milestone payments of up to $72.0 million and low double-digit to high-teens tiered royalties based on annual net sales of KarXT in the Licensed Territory, subject to reduction under specified circumstances. Receipt of sales milestone payments and royalties are not contingent on any further participation by the Company in the development of KarXT in the Licensed Territory.

The Zai License Agreement will expire upon the latest of the following dates with respect to the last licensed product in any region in the Licensed Territory: (i) the date of expiration of the last valid claim covering such licensed product in such region, (ii) the date that is a specific period after the date of the first commercial sale of such licensed product in such region and (iii) the expiration date of any regulatory exclusivity for such licensed product in such region. Zai may terminate the Zai License Agreement for convenience, subject to the terms thereto, by providing written notice to the Company, which termination will be effective following a prescribed notice period. In addition, the Company may terminate the Zai License Agreement under specified circumstances if Zai or certain other parties challenge the Company's patent rights or if Zai or its affiliates fail to complete certain development activities with respect to the licensed product for a specified period of time, subject to specified exceptions. Either party may terminate the Zai License Agreement for the other party’s uncured material breach, with a customary notice and cure period, or insolvency.

After termination or expiration, the Company is entitled to retain a worldwide, exclusive, and perpetual license from Zai to exploit the licensed product, which license would be non-exclusive after expiration (but not termination), subject to a reasonable royalty to be agreed by the parties if terminated for the Company's uncured material breach.

Revenue Recognition

The Company concluded that the distinct units of account within the agreement are reflective of a vendor-customer relationship and therefore within the scope of ASC 606.

Under the provisions of ASC 606, the Company identified one performance obligation. The Company provided an exclusive license to intellectual property, bundled with the associated know-how and certain professional services that are not substantive.

Under the terms of the Zai License Agreement, Zai has the sole right to manufacture, or have manufactured, KarXT for use in development and commercialization in the Licensed Territory. At the election of Zai, the Company may supply KarXT to Zai at the fully burdened manufacturing cost plus a specified margin, as defined within the Zai License Agreement. This provision was determined to be an option to acquire additional goods or services at a price that approximates the stand-alone selling price for that good or service, and therefore does not represent a material right, or separate performance obligation, within the context of the Zai License Agreement. For the year ended December 31, 2022, the Company recognized less than $0.1 million in revenue associated with sales of clinical drug supply to Zai. For the year ended December 31, 2021, no revenue was recognized for sales of clinical drug supply.

The Company determined the transaction price of the Zai License Agreement was equal to $37.0 million, which includes the upfront fee of $35.0 million and payments to taxing authorities on the Company's behalf. In estimating the stand-alone selling price, the Company determined that there were no significant financing components, noncash consideration or amounts that may be refunded to the customer, and as such the total unconstrained consideration of $37.0 million was included in the total transaction price.

License of Intellectual Property. The license to the Company's intellectual property represents a distinct performance obligation. The license and associated know-how was transferred to Zai in the fourth quarter of 2021 to satisfy this performance obligation. The Company allocated the full transaction price to the license of the Company's intellectual property and accordingly recognized revenue of $37.0 million as license revenue in its Consolidated Statement of Operations for the year ended December 31, 2021.

Milestone Payments. The potential development and regulatory milestone payments, as well as sales milestone payments, are paid upon achievement of certain milestones as defined in the Zai License Agreement. For the year ended December 31, 2022, the Company recognized $10.6 million in license revenue for certain development milestones and related payments to taxing authorities on the Company's behalf, and recorded $1.1 million in foreign tax expense to income tax provision. For the year ended December 31, 2021, no revenue was recognized for development and regulatory milestones.

For all remaining development and regulatory milestones, which, as of December 31, 2022, can total up to $70.0 million, it was determined that their achievement is highly dependent on factors outside of the Company's control. These payments have been fully constrained until the Company concludes that achievement of the milestone is probable, and that recognition of revenue related to the milestone will not result in a significant reversal in amounts recognized in future periods, and as such have been excluded from the transaction price. At the end of each subsequent reporting period, the Company will re-evaluate the probability of achievement of each milestone and any related constraint and, if necessary, adjust its estimate of the overall transaction price.

As of December 31, 2022, the Company has not recognized any revenue associated with sales milestones.

Royalties. Any consideration related to royalties will be recognized if and when the related sales occur, as they were determined to relate predominantly to the license granted to Zai and, therefore, have also been excluded from the transaction price. No royalty revenue was recognized during the years ended December 31, 2022 and 2021.

There was no deferred revenue as of December 31, 2022 or 2021 related to the Zai License Agreement.

Note 7. 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, 2022, 2021 and 2020 (in thousands, except share and per share data):

	Year Ended December 31,		
	2022	**2021**	**2020**
Net Loss	$ (276,336)	$ (143,805)	$ (68,554)
Weighted-average shares used in computing net loss per share	31,629,013	29,138,915	26,446,006
Net loss per share, basic and diluted	$ (8.74)	$ (4.94)	(2.59)

The Company’s potentially dilutive securities, which consist of stock options, 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.

Common Stock Equivalents

As of December 31, 2022, 2021 and 2020, stock options outstanding to purchase common stock of 5,570,355, 5,323,162 and 4,612,790, respectively, have been excluded from the calculation of diluted net loss per share because including them would have had an anti-dilutive impact.

Note 8. 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 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, 2022, there were 2,134,197 options outstanding under the 2009 Plan.

In May 2019, the Company's 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, restricted stock units ("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 of common stock that may be issued under the 2019 Plan 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, 2022, there were 1,720,906 common shares available for issuance and 3,436,158 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. 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, 2021	5,323,162	$ 50.04	7.7	$ 431,456
Granted	1,031,835	132.29		
Exercised	(691,719)	53.26		
Forfeited	(92,923)	113.48		
Outstanding as of December 31, 2022	5,570,355	$ 63.82	7.2	$ 744,097
Options vested and expected to vest as of December 31, 2022	5,570,355	$ 63.82	7.2	$ 744,097
Options exercisable as of December 31, 2022	3,538,587	$ 31.86	6.4	$ 582,594

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, 2022.

As of December 31, 2022, there was $125.3 million of unrecognized compensation cost, which is expected to be recognized over a weighted-average period of 2.8 years.

The weighted-average fair values of options granted during the years ended December 31, 2022, 2021 and 2020 was $79.63, $71.40, and $52.60, respectively. The intrinsic value of options exercised during the years ended December 31, 2022, 2021 and 2020 was $106.3 million, $40.5 million and $86.0 million, respectively.

The fair value of options granted was estimated at the date of grant using the Black-Scholes model with the following assumptions:

	Year Ended December 31,		
	2022	2021	2020
Expected term (in years)	5.50 - 7.00	5.50 - 7.00	5.50 - 7.00
Expected volatility	56.25% - 60.39%	56.57% - 60.21%	55.73% - 61.28%
Risk-free interest rate	1.47% - 4.19%	0.57% - 1.37%	0.35% - 1.49%
Expected dividend yield	0.00%	0.00%	0.00%

Stock-based Compensation Expense

Stock-based compensation expense is classified in the statements of operations for the years ended December 31, 2022, 2021 and 2020 as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
General and administrative	$ 26,509	$ 18,175	$ 9,704
Research and development	20,942	11,636	3,767
Total stock-based compensation expense	$ 47,451	$ 29,811	$ 13,471

Note 9. Fair Value of Financial Assets and Liabilities

Cash Equivalents and Investment Securities

The following table presents information about the Company's assets as of December 31, 2022 and 2021 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, 2022 Using			
	Level 1	Level 2	Level 3	Total
Cash equivalents:				
Money market fund	$ 160,158	$ —	$ —	$ 160,158
Commercial paper	—	61,277	—	61,277
Investment securities:				
US Treasuries	423,688	—	—	423,688
US government agencies	210,188	—	—	210,188
Corporate debt securities	—	63,728	—	63,728
Commercial paper	—	178,111	—	178,111
Total	$ 794,034	$ 303,116	$ —	$ 1,097,150

	Fair Value Measurement at December 31, 2021 Using			
	Level 1	Level 2	Level 3	Total
Cash equivalents:				
Money market fund	$ 199,019	$ —	$ —	$ 199,019
Investment securities:				
US Treasuries	100,043	—	—	100,043
Corporate debt securities	—	55,744	—	55,744
Commercial paper	—	131,251	—	131,251
Total	$ 299,062	$ 186,995	$ —	$ 486,057

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, 2022			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
US Treasuries (due within one year)	$ 329,533	$ 17	$ (2,044)	$ 327,506
US Treasuries (due after one year and less than three years)	96,802	—	(620)	96,182
US government agencies (due within one year)	178,319	54	(108)	178,265
US government agencies (due after one year and less than three years)	32,104	—	(181)	31,923
Corporate debt securities (due within one year)	51,952	1	(170)	51,783
Corporate debt securities (due after one year and less than three years)	11,983	—	(38)	11,945
Commercial paper (due within one year)	178,312	16	(217)	178,111
Total	$ 879,005	$ 88	$ (3,378)	$ 875,715

	December 31, 2021			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
US Treasuries (due within one year)	$ 15,137	$ —	$ (12)	$ 15,125
US Treasuries (due after one year and less than two years)	85,277	—	(359)	84,918
Corporate debt securities (due within one year)	45,510	—	(57)	45,453
Corporate debt securities (due after one year and less than two years)	10,338	—	(47)	10,291
Commercial paper (due within one year)	131,273	5	(27)	131,251
Total	$ 287,535	$ 5	$ (502)	$ 287,038

The Company has classified 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.

The Company is required 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, 2022 and 2021.

Note 10. Commitments and Contingencies

Leases

In March 2021, the Company entered into an agreement (“High Street Lease”) to sublease from a third party approximately 25,445 square feet of office space on High Street in Boston, Massachusetts, beginning on April 1, 2021 and expiring December 31, 2025. The initial fixed rental rate is $60 per rentable square foot of the premises per annum and will increase at a rate of $1 per rentable square foot each year, with base rent first becoming due on July 1, 2021. Upon signing of the High Street Lease, the Company was also required to pay the first full monthly installment of base rent of $0.1 million and a security deposit of $0.4 million. The security deposit was recorded within other non-current assets on the consolidated balance sheets as of December 31, 2022 and 2021. The first monthly installment was included as an adjustment to the ROU asset recognized upon commencement of the lease. The Company recognized an ROU asset and corresponding lease liability of $6.2 million and $6.0 million, respectively, on its consolidated balance sheet as of April 1, 2021, upon commencement of the High Street Lease.

The Company also has approximately 11,225 square feet of office space on Arch Street in Boston, MA ("Arch Street Lease Agreement") and 5,050 square feet of office space in Carmel, Indiana (“Indiana Lease Agreement”). The Arch Street Lease Agreement expires in December 2023, as amended, and the associated space is entirely subleased to third parties through the remainder of the current lease term ("Arch Street Subleases"). Under the terms of the Arch Street Lease Agreement, the Company is required to maintain a cash balance of $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, 2022 and 2021. Upon signing of the Arch Street Subleases, the Company received a security deposit of $0.1 million which has been recorded within restricted cash on the consolidated balance sheets as of December 31, 2022 and 2021. The Indiana Lease Agreement expires in July 2023, with the option to renew for an additional three-year term.

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.

The components of lease cost were as follows (dollar amounts in thousands):

	Year Ended December 31,		
	2022	2021	2020
Lease Cost:			
Operating lease cost	$ 2,150	$ 1,829	$ 791
Short-term lease cost	—	—	—
Sublease income	(580)	(254)	—
Total lease cost	$ 1,570	$ 1,575	$ 791
Other Information:			
Cash paid for amounts included in the measurement of lease liabilities	$ 2,547	$ 1,618	$ 733
Operating lease liabilities arising from obtaining right-of-use assets	—	6,040	3,259
Weighted-average remaining lease term	2.65 years	3.50 years	2.94 years
Weighted-average discount rate	5.87%	5.90%	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, 2022 (in thousands):

Year ended:		
December 31, 2023	$	2,520
December 31, 2024		1,597
December 31, 2025		1,622
Total future minimum lease payments		5,739
Less imputed interest		(411)
Present value of lease liabilities	$	5,328

The annual undiscounted cash flows to be received from subleases is $0.6 million as of December 31, 2022. The Amended Arch Street Lease Agreement, the Arch Street Original Premises, and Arch Street Expansion Premises mature in December 2023 and will not be extended.

Historically, all Company assets and liabilities belonged to a single corporate office asset group. The circumstances described above triggered a reassessment of asset grouping, such that the ROU assets associated with the Arch Street Lease Agreement had their own separately identifiable cash flows and therefore their own separate asset grouping. Sublease income associated with the Arch Street Subleases is projected to be lower than lease payments owed by the Company for this space, and therefore impairment was indicated for this new asset group. The carrying value of these ROU assets immediately before impairment was $2.0 million, and the fair value of these operating lease ROU assets immediately subsequent to the impairment, calculated as the present value of the estimated future cash flows attributable to the assets, was $1.3 million. The Company recognized $0.7 million in impairment losses on ROU assets within other income, net, on the statement of operations for the year ended December 31, 2021.

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 and Company ("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 package 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, 2022, 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 the Company receives 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.

The Company incurred no expenses related to the Patent License Agreement during the year ended December 31, 2022. During the year ended December 31, 2021, the Company paid less than $0.1 million in sublicense income associated with the Zai License Agreement to PureTech Health. In December 2020, the Company paid $2.0 million to PureTech Health, having reached the milestone of Phase 3 clinical trial commencement. As of December 31, 2022, the remaining development and regulatory milestone payments under the Patent License Agreement total up to $8.0 million. The Company had no outstanding liabilities to PureTech Health related to the Patent License Agreement at December 31, 2022 and 2021.

Other Funding Commitments

The Company enters 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, which are generally cancelable upon prior written notice. Payments due upon cancellation may consist of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation, and may also include termination penalties. As of December 31, 2022 and 2021, we had no outstanding liabilities related to such items.

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, 2022.

Note 11. Income Taxes

The Company recorded income tax expense of $1.4 million during the year ended December 31, 2022, and less than $0.1 million during each of the years ended December 31, 2021 and 2020. The Company did not recognize any significant deferred tax expense for the years ended December 31, 2022, 2021, or 2020 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,		
	2022	**2021**	**2020**
Statutory tax rate	21.0%	21.0%	21.0%
State taxes, net of federal benefit	7.3%	5.3%	10.3%
Share-based compensation	5.6%	3.6%	21.3%
Foreign withholding tax	-0.3%	0.0%	0.0%
Tax credits	8.2%	5.2%	3.2%
Change in valuation allowance	-42.2%	-35.1%	-55.7%
Other	-0.1%	0.0%	-0.1%
Effective income tax rate	**-0.5%**	**0.0%**	**0.0%**

Significant components of the Company's deferred tax assets and liabilities at December 31, 2022 and 2021 are as follows (in thousands):

	December 31,	
	2022	**2021**
Deferred tax assets:		
Operating tax losses	$ 105,911	$ 82,740
Capitalized research and development expenses	59,654	—
Tax credit carryforwards	38,840	13,695
Share-based compensation	18,457	11,699
Accrued expenses	2,745	1,653
Lease liability	1,371	1,910
Charitable contributions	188	10
Depreciation and amortization	10	—
Deferred tax assets	227,176	111,707
Valuation allowance	(225,973)	(110,046)
Deferred tax liabilities:		
ROU assets	(1,203)	(1,643)
Depreciation	—	(18)
Deferred tax liabilities	(1,203)	(1,661)
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. The Company was historically a subsidiary of PureTech Health. 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, the Company has filed separate state income tax returns subsequent to this date.

At December 31, 2022, on a separate return method, the Company has federal net operating loss carryforwards totaling $406.5 million, of which $9.8 million begin to expire in 2029 and the remaining $396.7 million can be carried forward indefinitely. In addition, the Company had state net operating loss carryforwards totaling $321.5 million which begin to expire in 2030. Lastly, the Company has federal research credits of $34.9 million and state research credits of $4.9 million which begin to expire in 2031. Because the Company had historically been a subsidiary of PureTech Health, $406.0 million and $301.5 million of the federal and state net operating loss carryforwards, respectively, can be used to offset income on the Company's future tax returns. In addition, $34.8 million and $4.9 million of the federal and state tax credit carryforwards, respectively, can be used to offset tax due on the Company's future tax returns. The Company's 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, research and development expenses capitalized under Internal Revenue Code Section 174, 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, 2022. The valuation allowance increased by $115.9 million during the year ended December 31, 2022, which primarily relates to the current year operating loss, expenses capitalized under Section 174, 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 assessed its potential Section 382 limitations during the year ended December 31, 2022, 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, 2022, 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, 2022, the Company has not accrued interest or penalties related to any uncertain tax positions.

The Company is 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 12. 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 $1.0 million for the year ended December 31, 2022, $0.5 million for the year ended December 31, 2021 and $0.2 million for the year ended December 31, 2020.

Note 13. Subsequent Events

In January 2023, the Company entered into an exclusive license agreement (the "GFB Agreement"), with GFB (ABC), LLC ("GFB"), assignee of the assignment estate of Goldfinch Bio, Inc., pursuant to which GFB granted to the Company the exclusive right and license to develop, manufacture, and commercialize GFB's TRPC4/5 candidates (the "GFB Compounds"), including the lead clinical-stage candidate known as KAR-2618 (formerly GFB-887). The Company agreed to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize at least one licensed product that contains or comprises a GFB Compound in at least two indications in the United States.

Under the terms of the GFB Agreement, the Company paid to GFB a $15 million upfront payment, and agreed to pay a total of up to $520.0 million for each GFB Compound upon the achievement of certain development, regulatory and commercial milestones with respect to such GFB Compound, of which $110.0 million, $150.0 million, and $260.0 million are related to development, regulatory, and commercial sales milestones, respectively. The Company also agreed to pay GFB a flat low-single digit royalty on aggregate net sales of each licensed product on a country-by-country basis until the expiration of the applicable royalty term, which ends on the later of (i) the expiration date of the last valid claim covering the licensed product in such country, (ii) the expiration date of regulatory exclusivity with respect to such licensed product in such country, and (iii) the date that is a specific period after the first commercial sale of such licensed product in such country. The royalty rate is subject to reduction on a licensed product-by-licensed product and country-by-country basis under certain circumstances. In the event that the Company sublicenses to a third party any of the rights to the licensed intellectual property granted under the GFB Agreement, the Company will be obligated to pay GFB royalties within the range of 25% to 35% on any consideration the Company receives from the sublicensee, excluding royalties and certain other payments.

Unless earlier terminated, the GFB Agreement will expire on the expiration of the last to expire royalty term. Unless the GFB Agreement is earlier terminated, on expiration of each applicable royalty term, the Company will have a fully paid-up, irrevocable and perpetual license to develop, manufacture and commercialize each applicable licensed product in the applicable country. Either party may terminate the GFB Agreement for the other party's material breach, following a customary notice and cure period, or insolvency. The Company may terminate the GFB Agreement for any reason upon 90 days written notice to GFB.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

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, 2022. 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, 2022.

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, 2022 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, 2022.

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, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

Not applicable.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

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 2023 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 2023 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 2023 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 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Our independent public accounting firm is KPMG LLP, Boston, Massachusetts, PCAOB Auditor ID 185.

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 2023 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 Stockholders' Equity
- 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.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

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 3.1 to the Registrant's Quarterly Report on Form 10-Q, filed with the SEC on May 6, 2021, 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)

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)
10.22	Sublease, dated as of March 5, 2021, between the Registrant and Workable, Inc. (filed as Exhibit 99.1 to the Registrant's 8-K, filed with the SEC on March 10, 2021)
10.23+	License Agreement, dated as of November 8, 2021, between the Registrant and Zai Lab (Shanghai) Co., Ltd. (filed as Exhibit 10.23 to the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.24#	Employment Agreement, dated as of November 29, 2021, between the Registrant and Charmaine Lykins (filed as Exhibit 10.24 to the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.25#	Employment Agreement, dated November 30, 2022, by and between the Company and William Meury (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 6, 2022)
10.26*+	License Agreement, dated as of January 31, 2023, between the Registrant and GFB (ABC), LLC
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)

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* 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 23, 2023

By: /s/ William Meury
William Meury
President and Chief Executive Officer
(Principal Executive Officer)

Date: February 23, 2023

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/ William Meury William Meury	President, Chief Executive Officer and Director (Principal Executive Officer)	February 23, 2023
/s/ Troy Ignelzi Troy Ignelzi	Chief Financial Officer (Principal Financial and Accounting Officer)	February 23, 2023
/s/ Christopher J. Coughlin Christopher J. Coughlin	Director	February 23, 2023
/s/ James I. Healy, M.D. James I. Healy, M.D.	Director	February 23, 2023
/s/ Jeffrey M. Jonas, M.D. Jeffrey M. Jonas, M.D.	Director	February 23, 2023
/s/ Laurie J. Olson Laurie J. Olson	Director	February 23, 2023
/s/ Atul Pande, M.D. Atul Pande, M.D.	Director	February 23, 2023
/s/ Steven Paul, M.D. Steven Paul, M.D.	Chief Scientific Officer, President of Research and Development, and Director	February 23, 2023
/s/ Denice M. Torres Denice M. Torres	Director	February 23, 2023
/s/ David E. Wheadon, M.D. David E. Wheadon, M.D.	Director	February 23, 2023

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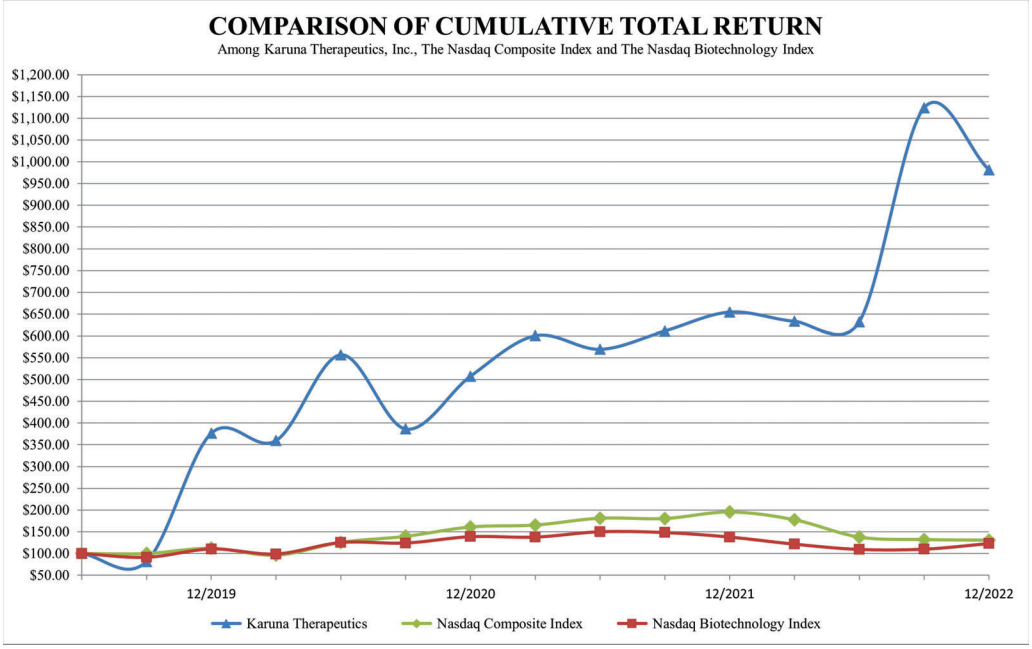
Karuna Therapeutics Stock Performance Graph



The graph above shows a comparison from June 28, 2019 through December 31, 2022 of cumulative total return on assumed investment of $100.00 in cash in our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance.

Executive Officers

Bill Meury
President and Chief Executive Officer

Stephen Brannan, M.D.
Chief Medical Officer

Troy Ignelzi
Chief Financial Officer

William Kane
Chief Commercial Officer

Andrew Miller, Ph.D.
Founder and Chief Operating Officer

Steven Paul, M.D.
Chief Scientific Officer and President of Research and Development

Board of Directors

Christopher J. Coughlin, *Chairman of the Board*

James Healy, M.D., Ph.D.

Jeffrey Jonas, M.D.

Bill Meury, *President and Chief Executive Officer*

Laurie Olson

Atul Pande, M.D.

Steven Paul, M.D., *Chief Scientific Officer and President of Research and Development*

Denice Torres

David Wheadon, M.D.

2023 Annual Meeting of Stockholders

June 20, 2023, 9:00 a.m., Eastern Time
Virtual meeting only via webcast at
www.virtualshareholdermeeting.com/KRTX2023

Transfer Agent and Registrar

American Stock Transfer & Trust Company, LLC
6201 15th Avenue
Brooklyn, NY 11219

Investor Relations

investors@karunatx.com

Exchange Listing

Nasdaq Global Market (Ticker: KRTX)

Principal Corporate Office

99 High Street, Floor 26
Boston, MA 02110

Independent Registered Public Accounting Firm

KPMG LLP
Boston, Massachusetts

www.karunatx.com

This annual report contains forward looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding our expectations about the timing of our planned regulatory filings, our goals to develop and commercialize our product candidates, and our liquidity and capital resources. Forward looking statements are not promises or guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in such forward-looking statements. These factors include risks related to our limited operating history, our ability to obtain necessary funding, our ability to generate positive clinical trial results for our product candidates and other risks inherent in clinical development, the timing and scope of regulatory approvals, changes in laws and regulations to which we are subject, competitive pressures, our ability to identify additional product candidates, risks relating to business interruptions resulting from the coronavirus (COVID-19) pandemic, and other risks set forth under the heading "Risk Factors" of our Annual Report on Form 10-K for the year ended December 31, 2022 and in our subsequent filings with the Securities and Exchange Commission. Our actual results could differ materially from the results described in or implied by such forward looking statements. Forward-looking statements speak only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise these forward-looking statements.