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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2020
OR

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

For the transition period from _____ to_____
Commission File No. 001-38535

APTINYX INC.

(Exact name of registrant as specified in its charter)

Delaware	**47-4626057**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

909 Davis Street, Suite 600
Evanston, IL 60201
(847) 871-0377

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.01 per share	**APTX**	**Nasdaq Global Select Market**

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

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

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

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

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

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

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

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

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

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

As of June 30, 2020, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $195 million based upon the closing sale price of our common stock of $4.17 on that date.

As of March 15, 2021, there were 66,889,625 shares of the registrant's common stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2021 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2020. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

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SUMMARY OF RISK FACTORS

The following is a summary of the principal risks described below in Part I, Item 1A "Risk Factors" in this Annual Report on Form 10-K. We believe that the risks described in the "Risk Factors" section are material to investors, but other factors not presently known to us or that we currently believe are immaterial may also adversely affect us. The following summary should not be considered an exhaustive summary of the material risks facing us, and it should be read in conjunction with the "Risk Factors" section and the other information contained in this Annual Report on Form 10-K.

Risks related to our business, financial position, and need for additional capital

- We are a clinical-stage biopharmaceutical company with no products approved for commercial sale.
- We have incurred significant operating losses since our inception and anticipate we will incur continued losses for the foreseeable future, and we may never generate revenue or be profitable.
- We will need to raise additional capital.
- The COVID-19 pandemic may materially and adversely affect our business and our financial results.

Risks related to product development

- We may not be successful in our efforts to continue to create a pipeline of product candidates or to develop commercially successful products. We may fail to expend our limited resources on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.
- We have concentrated our research and development efforts on the treatment of disorders of the brain and nervous system, a field that has seen limited success in drug development. Further, our product candidates are based on new approaches and novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.
- We may encounter difficulties in commencing or completing our clinical studies, or in enrolling subjects in our clinical studies, thereby delaying or preventing development of our product candidates.
- Our clinical studies may fail to demonstrate adequate safety and efficacy of our product candidates, which would prevent, delay, or limit the scope of regulatory approval and commercialization.

Risks related to regulatory approval and other legal compliance matters

- The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time-consuming, and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, we will be unable to generate product revenue and our business will be substantially harmed.
- If any of our product candidates obtain regulatory approval, additional competitors could enter the market with generic versions of such drugs, which may result in a material decline in sales of affected products.
- Our employees, independent contractors, consultants, commercial partners, and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements or violations of the U.S. Foreign Corrupt Practices Act, or FCPA, and other worldwide anti-bribery laws.

Risks related to our reliance on third parties

- We rely, and expect that we will continue to rely, on third parties to conduct any clinical studies for our product candidates and on third party suppliers to manufacture our clinical drug supplies for our product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

- We are dependent on single-source suppliers for some of the components and materials used in, and the processes required to develop, our product candidates. Our use of single-source suppliers of raw materials, components, key processes, and finished goods exposes us to several risks, including disruptions in supply, price increases, or late deliveries.

Risks related to our intellectual property rights

- If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our product candidates, others could compete against us more directly by developing and commercializing products similar or identical to ours, which would have a material adverse impact on our business, results of operations, financial condition, and prospects. Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

General company-related risks

- Our future success depends on our ability to retain our management team and to attract, retain, and motivate qualified personnel.

- Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

Risks related to our common stock

- Market volatility may affect our stock price and the value of your investment.

- Our principal stockholders and management own a significant percentage of our stock and, if they choose to act together, will be able to control or exercise significant influence over matters subject to stockholder approval, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control.

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

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains forward-looking statements, which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “designed,” “project,” “should,” “target,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments that we may make or enter into.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We are responsible for all of the disclosure contained in this Annual Report on Form 10-K, and we believe these industry publications and third-party research, surveys and studies are reliable.

PART I

Unless the context requires otherwise, references in this Annual Report on Form 10-K to the "Company," "Aptinyx," "we," "us," and "our" refer to Aptinyx Inc. Our "board of directors" refers to the board of directors of Aptinyx Inc.

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel, proprietary, synthetic small molecules for the treatment of brain and nervous system disorders. We focus our efforts on targeting and modulating N-methyl-D-aspartate receptors, or NMDArs, which are vital to normal and effective function of the brain and nervous system. We believe leveraging the therapeutic advantages of the differentiated modulatory mechanism of our compounds will drive a paradigm shift in the treatment of disorders of the brain and nervous system.

We are advancing a pipeline of distinct product candidates derived from our NMDAr modulator discovery platform, or the discovery platform. NYX-2925 is in Phase 2 clinical development for the treatment of chronic pain. NYX-2925 is being evaluated in two Phase 2b studies in two chronic pain conditions: one evaluating the efficacy and safety in approximately 200 patients with painful diabetic peripheral neuropathy, or painful DPN, and the other evaluating the efficacy and safety in approximately 300 patients with fibromyalgia. Following a temporary pause in enrollment in March 2020 due to challenges introduced by the COVID-19 pandemic, both of these studies have now recommenced and are currently enrolling patients. NYX-783 is in Phase 2 clinical development for the treatment of post-traumatic stress disorder, or PTSD. In October 2020, we announced data from an exploratory Phase 2 study of NYX-783 in patients with PTSD. In the study, patients treated with NYX-783 demonstrated improvements across PTSD symptoms and NYX-783 was well-tolerated with no drug-related serious adverse events reported. While the exploratory study was not powered to detect statistically significant differences between NYX-783 and placebo, on some measures NYX-783 did demonstrate statistically significant separation. NYX-458 is in Phase 2 clinical development for the treatment of cognitive impairment associated with Parkinson's disease and Lewy body dementia. We initiated an exploratory Phase 2 study of NYX-458 in patients with cognitive impairment associated with Parkinson's disease in December 2019. Due to challenges introduced by the COVID-19 pandemic, we suspended enrollment of new patients in this study in March 2020. We have incorporated various changes to the protocol in order to minimize the potential impact of COVID-19 on the conduct of the study, changes that we believe will also optimize the chances to detect efficacy signals on the neurocognitive measures in the study. In recent months we have resumed study activities and we expect to recommence screening of patients for inclusion in the study in the coming weeks.

Our discovery platform is based on extensive original research into a novel way of modulating NMDArs. NMDArs are a subclass of receptors for glutamate, the principal excitatory neurotransmitter in the brain. Our molecules bind in a previously uncharacterized binding domain, or "pocket", on NMDArs that is distinct from that of other NMDAr-targeted therapies. The mechanism by which our molecules modulate NMDArs triggers a cascade of activity that ultimately strengthens the synaptic connections between neural cells, resulting in stronger connections over time between these cells. The communication between neural cells is not only essential to routine function of the nervous system, but also allows the cells of the nervous system to learn, or adapt in response to external stimuli, through a process called synaptic plasticity. We believe our therapeutic approach, which modulates NMDArs to enhance synaptic plasticity, affecting learning and memory, holds great promise for alleviating multiple disorders of the brain and nervous system, such as cognitive impairment, PTSD, chronic pain, and depression.

The foundation of our proprietary discovery platform is the ability to modulate NMDArs in a highly specific and selective manner to enhance synaptic plasticity. Rather than fully turning the receptor "on" (agonism) or "off" (antagonism), we believe our approach effectively normalizes NMDAr function, enhancing communication between neural cells and avoiding the issues associated with excessive unidirectional activation or inhibition that have limited NMDAr-targeted drug development historically.

In clinical studies, compounds generated from our discovery platform penetrate the blood brain barrier to achieve brain concentration levels consistent with levels observed at doses that had significant effects in various preclinical animal models. These product candidates are orally bioavailable, potentially suitable for once-daily dosing, and have favorable tolerability profiles with little to no significant adverse events in studies completed to date. We believe these clinical data suggest that product candidates from our discovery platform may have wide dose ranges that are both safe and effective.

Our Strategy

Our goal is to become a leading biopharmaceutical company in the discovery, development, and commercialization of innovative therapies for disorders of the brain and nervous system with significant unmet medical needs. Key elements of our strategy are to:

- **Advance the development of NYX-2925 as a novel treatment for chronic centralized pain conditions.** We believe NYX-2925, if approved, could be an important potential therapy for chronic pain with mechanistic innovations that address significant unmet medical needs. Across all Phase 1 and Phase 2 studies of NYX-2925 completed to date, it has been well tolerated with no drug-related serious adverse events reported. We have completed two Phase 2 studies of NYX-2925. In our completed Phase 2 study in painful diabetic peripheral neuropathy, or DPN, NYX-2925 demonstrated analgesic activity. Further, in our completed Phase 2 fibromyalgia neuroimaging biomarker study, NYX-2925 demonstrated relevant brain activity and analgesic activity. Together, data from these first-in-patient studies inform and support the future development of NYX-2925 for the treatment of chronic pain, including our ongoing Phase 2b studies in painful DPN and fibromyalgia.

- **Advance the development of NYX-783 as a novel treatment for PTSD.** We believe NYX-783, if approved, could represent a transformative therapeutic option in PTSD that enhances the extinction learning processes involved in alleviating the traumatic response that persists in people with PTSD well after a traumatic event or experience, while also addressing the core symptoms and major comorbidities of the disorder. To date, we have completed a Phase 1 study and a Phase 2 study with NYX-783. Across both studies, NYX-783 has demonstrated a favorable tolerability profile with no drug-related serious adverse events reported. In the Phase 2 exploratory study, we observed encouraging activity on PTSD symptoms that form the basis for future evaluation and development of NYX-783 as a treatment for patients with PTSD.

- **Advance the development of NYX-458 as a novel treatment for cognitive impairment associated with Parkinson's disease and Lewy body dementia.** NYX-458 is currently in Phase 2 clinical development as a treatment for cognitive impairment. We expect our first-in-patient exploratory

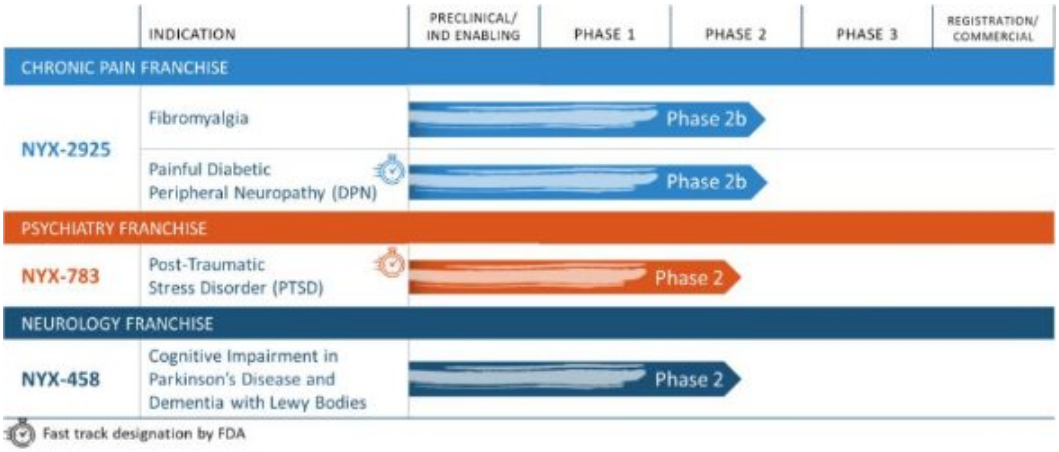
Phase 2 study of NYX-458, which is currently underway, will inform future development of NYX-458. Based on compelling data in a relevant, translatable, non-human primate model, we believe NYX-458, if approved, may offer substantial improvements over existing treatments for cognitive impairment associated with dementia with Lewy bodies.

- **Continue to expand our pipeline by leveraging our NMDAr modulator discovery platform, building on and extending our leadership in NMDAr biology.** We intend to use our discovery platform to develop a broad pipeline and product portfolio across an array of disorders of the brain and nervous system. Our pipeline is fueled by our library of over 1,000 unique, synthesized, small-molecule NMDAr modulators derived through our extensive original research and the discovery of a novel binding domain that we believe could allow for safe and effective enhancement of synaptic plasticity. All of these compounds have been designed to meet favorable central nervous system, or CNS, safety and pharmacokinetic, or PK, criteria. We also plan to continue seeking NMDAr-dependent biomarkers which could help to inform the development of our future product candidates.

- **Optimize the development and commercial potential of our product candidates.** We own the worldwide commercial rights to NYX-2925, NYX-783, and NYX-458 in our selected indications. Our primary strategy is to independently pursue the development and commercialization of our product candidates. We have assembled an experienced management team that is capable of executing along the entire value chain of drug development and commercialization. As we continue to build and develop our product portfolio, we may opportunistically pursue strategic partnerships that maximize the value of our pipeline.

Product Candidates From our Discovery Platform

The following table summarizes the current development status of our pipeline of wholly owned product candidates generated from our discovery platform:



While all of our product candidates and the other molecules from our discovery platform modulate NMDArs, they are distinct chemical entities with different pharmacologic properties. Each of our molecules binds uniquely within the binding domain, resulting in a variety of activity, potency, and NMDAr-subtype selectivity profiles. We evaluate the therapeutic implications of these variations by interrogating our molecules across different preclinical models of brain and nervous system disorders. The data we collect from these preclinical studies indicate which molecules are better suited for different indications and inform our development decisions accordingly.

NYX-2925 for the Treatment of Chronic Centralized Pain Conditions

NYX-2925 is a novel, oral, small molecule NMDAr modulator being developed for the treatment of chronic pain. NYX-2925 works by enhancing synaptic plasticity in the brain, a mechanism that is differentiated from any therapy currently used for the treatment of chronic pain. This approach is uniquely suited to treat centralized chronic pain as it is established that, when pain becomes chronic, it becomes increasingly centrally (brain) mediated. In normal pain processing, a stimulus is sensed by peripheral nerves and signal is relayed to the spinal cord, ultimately leading to the brain perceiving the stimulus as painful. When this process is experienced chronically, hyper-sensitivity and overactivity can emerge in the periphery, in the spinal cord, and in the brain. Changes in the brain include abnormalities in pain perception and processing pathways, and reduced descending inhibition of pain signals. These changes together can increase pain perception, including the perception of pain in the absence of normally painful stimuli. Beyond our lead indications for NYX-2925—painful DPN and fibromyalgia—additional chronic pain conditions have been associated with aberrant centralized pain processing and we believe the mechanism of action of NYX-2925 makes it a promising therapeutic candidate for the treatment of numerous chronic pain conditions.

Painful Diabetic Peripheral Neuropathy

The development of NYX-2925 in painful DPN has been granted Fast Track designation by the U.S. Food and Drug Administration, or FDA.

Prevalence and Market Opportunity

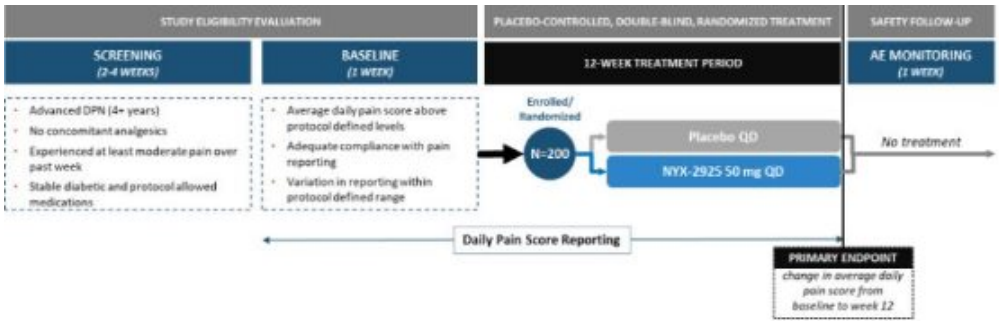
Painful DPN is one of the most common complications among people with diabetes. We estimate that of the nearly 30 million people in the United States with diabetes, approximately 5.5 million of them suffer from painful DPN. Painful DPN initially presents as peripheral nerve damage caused by sustained elevated glucose levels, resulting in highly localized pain in the hands and feet (often referred to as “glove and stocking” pain). As this pain persists, it has been shown that the processing of this pain moves from sensory regions in the brain to the emotional and learning and memory regions of the brain.

The current pharmacotherapies for painful DPN are antiepileptics, antidepressants, and opioids, all of which have significant drawbacks including limited efficacy in a broad patient population, substantial side effects, and risk of abuse or addiction. The limited efficacy and substantial side effects associated with these therapies leave substantial unmet medical need in treating these patients, and we believe NYX-2925, if approved, could offer meaningful improvements on both safety and efficacy in the treatment of painful DPN.

Phase 2b Clinical Study Currently in Progress

We initiated a Phase 2b clinical study of NYX-2925 in patients with painful DPN in 2019 and, following a temporary suspension of enrollment in March 2020 due to challenges posed by the COVID-19 pandemic, we recommenced this study in late December 2020. The Phase 2b study is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of NYX-2925 in patients with advanced DPN. The study is expected to enroll approximately 200 adult patients. Following a screening period, eligible patients will be randomized to receive oral doses of NYX-2925 50 mg or placebo once daily over the treatment period. The primary endpoint in the study is the change from baseline in average daily pain score over a 12-week period as reported on the 10-point numeric rating scale, or NRS. Multiple

secondary endpoints related to pain and patient quality of life will also be evaluated. The graphic below depicts the design of this ongoing Phase 2b study.

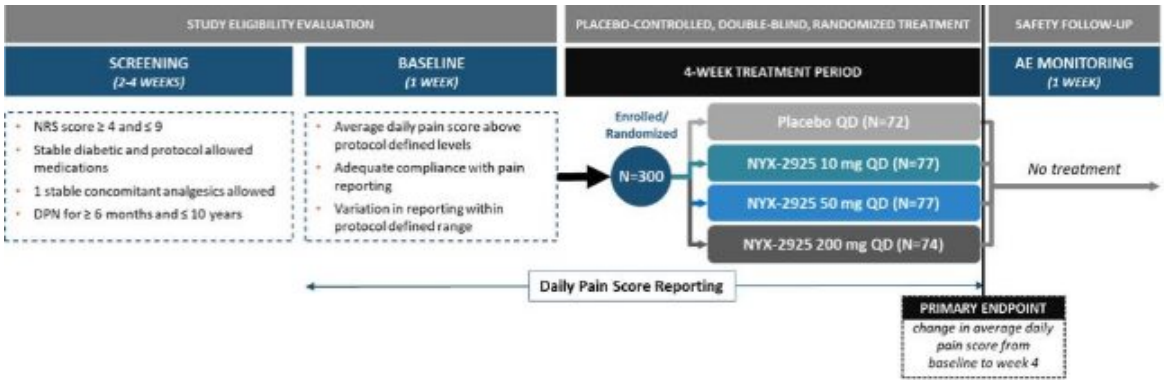


Completed Phase 2 Clinical Study

In January 2019, we completed a Phase 2 clinical study evaluating the safety and efficacy of NYX-2925 in adult patients with painful DPN. The data generated from this study inform and support future development of NYX-2925 for the treatment of chronic pain, specifically with regard to the appropriate dose, patient population, and design to evaluate in future studies.

This initial Phase 2 study of NYX-2925 was a double blind, randomized, placebo-controlled study in 300 adult patients across 35 U.S.-based sites. Over the four-week treatment period, patients received daily oral doses of either placebo or NYX-2925. Placebo and multiple dose levels of NYX-2925 were evaluated, including 10 mg, 50 mg, and 200 mg. Patients were randomized in a 1:1:1:1 manner across the four arms of the study.

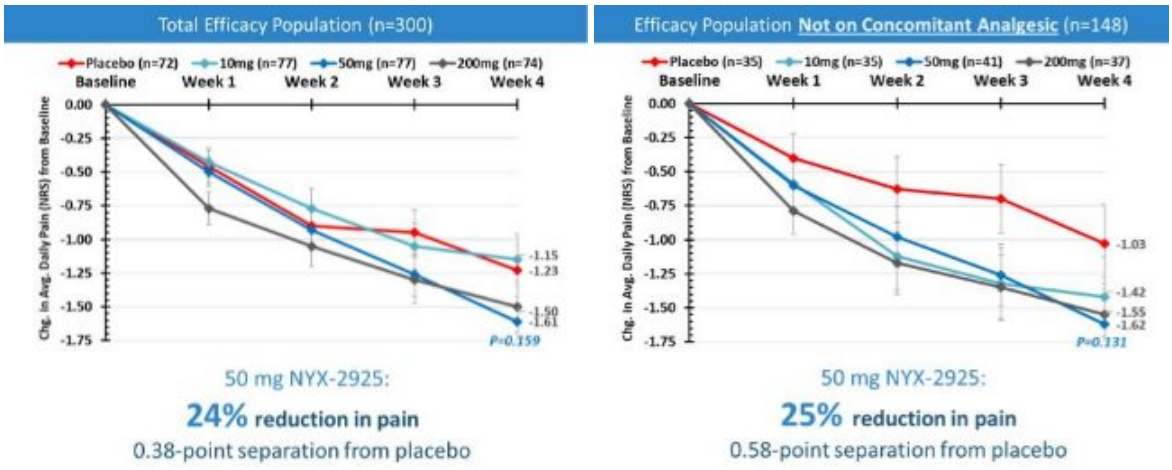
Pain was assessed using a patient reported scale (with a pain score ranging from zero to ten) and recorded daily on a provided hand-held device. The study assessed daily pain scores at baseline (for seven days prior to treatment) and throughout the study duration with the primary endpoint being the change in pain score from baseline to week four, the final week of treatment. Additional endpoints measured a range of other physical and psychological parameters.



Results

NYX-2925 exhibited a favorable tolerability profile with only placebo-like side effects and no treatment-related serious adverse events. Of the three dose levels evaluated, the 50 mg dose showed the most robust improvements across multiple measures—consistent with previous clinical and preclinical data suggesting the potential for an inverted "U-shaped" dose response with this mechanism. Importantly, the 50 mg dose did not appear to have plateaued in effect by week four, suggesting that a longer treatment period may result in continued improvement and larger drug effect. The graph on the

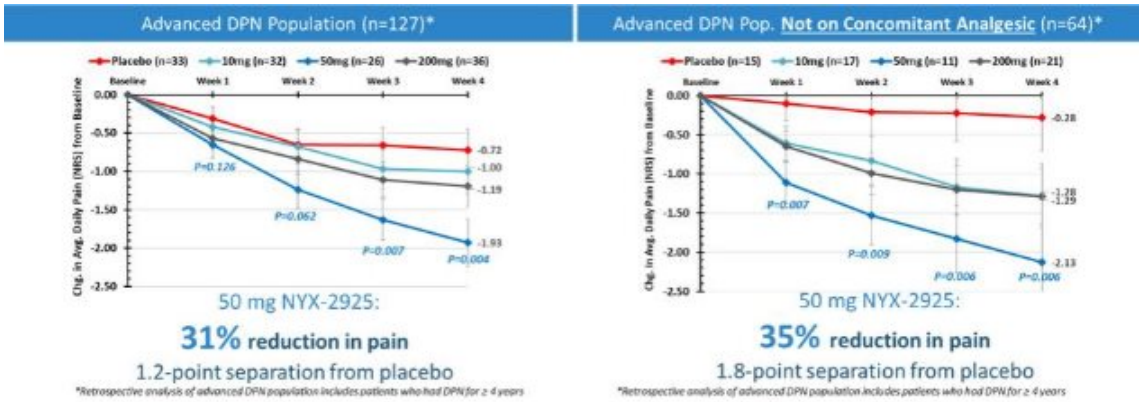
left below summarizes the top-line results in the total efficacy population (N=300) on the primary endpoint, average NRS pain score over the prior 24 hours, compared to placebo. While statistically significant separation from placebo was not achieved in the total study population, there was numeric separation from placebo and a clinically meaningful reduction in mean average daily pain score from baseline observed at week 4. Further, in a pre-specified analysis, patients not taking a concomitant analgesic medication (N=148) showed a greater separation on average daily pain scores from placebo. The graph on the right below shows the change in average pain compared to placebo in only those patients who were not taking a concomitant analgesic medication. Given that this was the first evaluation of NYX-2925 in patients with painful DPN, the p-values shown below are not adjusted for multiple comparisons.



Note: All changes reflect change from baseline in least squares mean using a mixed effects repeated measures model.

In March 2019, we announced results from the detailed analysis of the full dataset from the study, which identified a highly mechanistically relevant sub-group of patients in which NYX-2925 demonstrated a much greater treatment benefit. In this retrospective analysis, patients with advanced DPN, or DPN for four years or longer, showed statistically significant and clinically meaningful reductions in average daily pain and also showed consistent robust improvements across the other endpoints measured in the study. This sub-group of patients is particularly relevant to the mechanism by which NYX-2925 is proposed to act. It is established that, as pain becomes chronic, it becomes increasingly centrally mediated and characterized by disrupted central processing in the brain. We believe the proposed mechanism of NYX-2925 addresses the increasingly centralized pain perceived by advanced DPN patients when they experience prolonged chronic pain over a long period of time. This patient sub-group is not only mechanistically relevant, but also substantial in size, representing over 42% of the entire study population and allowing for rigorous analysis.

The graph on the left below depicts the change from baseline in average daily pain in the advanced DPN patient sub-group. Further, advanced DPN patients not taking a concomitant analgesic medication demonstrated even more pronounced separation from placebo.



Note: All changes reflect difference in least squares mean change from baseline using a mixed effects repeated measures model.

These significant improvements were observed consistently across other endpoints measured in the study, including worst daily pain, pain on walking, daily sleep interference, and others.

Based on the safety and efficacy profile exhibited in the study, we believe NYX-2925 has potential to address major unmet needs in the treatment of chronic pain.

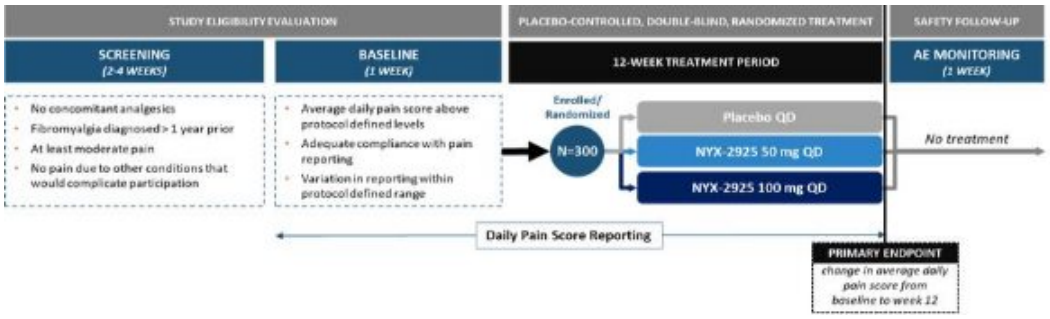
Fibromyalgia

Prevalence and market opportunity

Fibromyalgia is a chronic condition associated with widespread pain and tenderness, as well as general fatigue. Fibromyalgia is considered by many to be a condition that is largely mediated in the central nervous system, given that fibromyalgia sufferers often present without a direct peripheral insult or injury. People suffering from fibromyalgia also often experience sleep disruption, depressed mood, and cognitive impairment. It is estimated that, in the United States, fibromyalgia affects more than 5 million people. Currently, there are only three FDA-approved pharmacologic treatments for fibromyalgia, but they have limited efficacy and burdensome side effects in many patients.

Phase 2b Clinical Study Currently in Progress

In 2019 we initiated a Phase 2b clinical study of NYX-2925 in patients with fibromyalgia. Following the temporary suspension of enrollment in this study due to challenges posed by the COVID-19 pandemic, we recommenced enrollment in September 2020. The Phase 2b study is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of NYX-2925 in patients with fibromyalgia. The study is expected to enroll approximately 300 patients. Following a screening period, eligible patients will be randomized to receive oral doses of NYX-2925 50 mg, NYX-2925 100 mg, or placebo once daily over the treatment period. The primary endpoint in the study is the change from baseline in average daily pain score over a 12-week period as reported on the 10-point NRS. Multiple secondary endpoints related to pain, fatigue, cognitive performance, and patient quality of life will also be evaluated. The graphic below depicts the design of this ongoing Phase 2b study.



Completed Phase 2 Neuroimaging Biomarker Study

In June 2019, we completed a Phase 2 exploratory neuroimaging biomarker study in patients with fibromyalgia. The study was a single-blind, placebo-controlled study. We enrolled 22 adult patients across two academic sites in the U.S. evaluating daily doses of 20 mg and 200 mg.

The goal of the study was to determine whether daily dosing of NYX-2925 in patients with fibromyalgia changes certain biomarkers of central pain processing using various neuroimaging techniques, including fMRI. We also evaluated additional endpoints, including daily pain scores, and a range of other physical and psychological parameters. Each subject served as her own control, receiving both placebo and NYX-2925 over the course of the six-week study.

Results

We reported in June 2019 that administration of NYX-2925 resulted in statistically significant effects on the primary endpoint, brain activity biomarkers associated with central pain processing. Specifically, NYX-2925 was shown to reduce pain-evoked glutamate release in the insular cortex, significantly reduce combined glutamate and glutamine levels in the dorsal anterior cingulate cortex, and change other connectivity patterns associated with central pain processing. In aggregate, these data demonstrate that NYX-2925 has an antinociceptive profile and is acting in the brain on the specific markers that have been shown to be associated with fibromyalgia and centralized pain processing.

In addition to the positive results shown on the primary imaging endpoints, NYX-2925 also demonstrated statistically significant and clinically meaningful improvements on the secondary, patient-reported endpoints, including daily pain scores, fibromyalgia impact questionnaire, and fatigue. Importantly, in the study, NYX-2925 demonstrated a favorable tolerability profile with no drug-related serious adverse events reported and an overall placebo-like adverse event profile.

In November 2019, the results from this study were presented at the American College of Rheumatology Annual Meeting. The results from this study provide support to advance NYX-2925 in development for the treatment of fibromyalgia.

Future Development

We intend to advance NYX-2925 toward regulatory approval for the treatment of painful DPN and fibromyalgia. In addition, we intend to pursue broader chronic pain indications for NYX-2925, such as neuropathic lower-back pain and osteoarthritic pain.

In addition to pursing FDA approval in the United States in these indications, we also plan to explore registrations outside of the United States in the most significant markets, including but not limited to the European Union, Japan, Canada, Australia, and large emerging markets such as China.

NYX-783 for the Treatment of Post-Traumatic Stress Disorder

NYX-783 is a novel, oral, small-molecule NMDAr modulator in development for the treatment of post-traumatic stress disorder, or PTSD. Preclinical data suggest that NYX-783 may accelerate fear extinction and inhibit spontaneous fear recurrence, potentially addressing a key underlying learning and memory dysfunction associated with PTSD. In a Phase 1 study in healthy adult volunteers, NYX-783 demonstrated a predictable, dose dependent, and linear PK profile with no accumulation after multiple daily doses and was well-tolerated with no drug related serious adverse events. As evaluated through cerebral spinal fluid, or CSF, exposure, NYX-783 adequately crosses the blood brain barrier and achieves CNS concentration levels in line with the most efficacious preclinical doses with a similar plasma-to-brain concentration ratio as that observed in rats. In our exploratory Phase 2a study in patients with PTSD, completed in October 2020, a favorable tolerability profile and promising improvements across numerous PTSD symptoms were observed in patients receiving NYX-783. The data yielded by the studies completed to date suggest that NYX-783 has the potential to address numerous unmet medical needs in the treatment of PTSD. Following interaction with the FDA to discuss and align on the future development path for NYX-783, we expect to initiate a Phase 2b study of NYX-783 with a design consistent with that of a registration-supportive study.

The development of NYX-783 for the treatment of PTSD has been granted Fast Track designation by the FDA and we believe NYX-783, if approved, may represent a significant improvement over current treatments for PTSD.

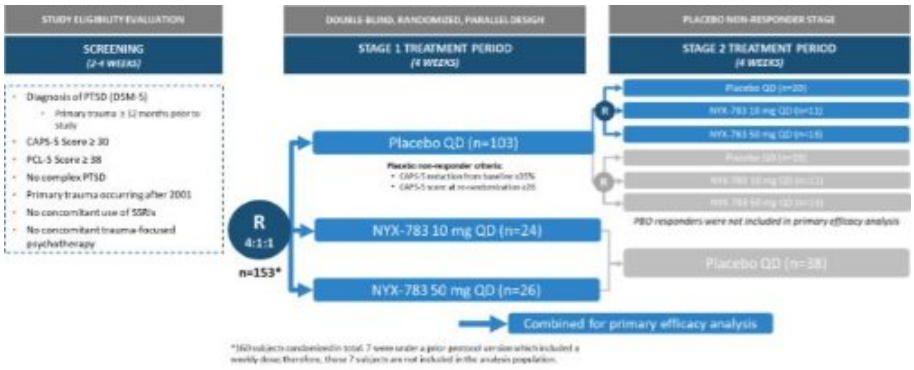
Prevalence and Market Opportunity

It is estimated that 8% to 10% of people that experience trauma will develop PTSD in their lifetime and approximately 8.5 million people currently suffer from PTSD in the United States. Many of these people are currently untreated or poorly treated due to the lack of safe and effective options. To date only two pharmacotherapies have been approved to treat PTSD and both are selective serotonin reuptake inhibitor, or SSRI, antidepressants that have limited efficacy in treating the symptoms of PTSD.

Completed Exploratory Phase 2 Clinical Study

In October 2020, we completed a Phase 2a exploratory study to evaluate the safety, efficacy, and pharmacokinetics of NYX-783 in patients with PTSD. The study was designed as an initial signal detection study to inform future development of NYX-783 with regard to the most appropriate dosing regimen, enrollment criteria, endpoints, and powering to best assess the overall effect of NYX-783 on PTSD symptoms. The study was a randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study and enrolled 160 adult patients. Seven of the patients were enrolled under a prior protocol version which included a weekly dose; therefore, those seven subjects were not included in the efficacy analysis population. After confirming eligibility and PTSD diagnosis, patients were randomly assigned to receive placebo, 10 mg NYX-783, or 50 mg NYX-783 once daily over the course of the study. The study consisted of two four-week treatment periods (Stage 1 and Stage 2) and no patient received NYX-783 for more than four weeks over the course of the study. The primary efficacy endpoint of the study was the improvement from baseline on the total score and symptom cluster scores of the Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, or the CAPS-5. The CAPS-5 measures a total score and individual scores for each PTSD symptom cluster (arousal & reactivity, negative cognitions (thoughts) & mood, intrusive memories, and avoidance), allowing us to evaluate the effects of NYX-783 on overall symptoms as well as the individual symptom domains.

The exploratory study leveraged a SPCD comprising two stages, each four weeks in duration. In Stage 1, patients were randomized to placebo, 10 mg NYX-783, or 50 mg NYX-783, with an overweighting to placebo. At the completion of Stage 1, placebo responders and non-responders were identified and segmented in a blinded fashion according to pre-specified response criteria and each group was then re-randomized to placebo, 10 mg NYX-783, or 50 mg NYX-783 in Stage 2. Patients who received NYX-783 in Stage 1 received placebo in Stage 2. The primary analysis population for efficacy in this study included the groups on NYX-783 and placebo from Stage 1 and the placebo non-responder group from Stage 2. The design of this study is depicted below.



This study was designed as an initial signal detection study with the aim of characterizing the safety and efficacy of NYX-783 to inform future development for the treatment of PTSD.

Results

Administration of NYX-783 resulted in encouraging data on multiple PTSD symptom scales evaluated in the study. In the study, the 50 mg NYX-783 group showed a clinically meaningful improvement from baseline on CAPS-5 Total score with a greater proportion of patients demonstrating a response than in the placebo group in addition to the signal observed on the CAPS-5 Total score. In addition, despite the study being powered based on clinical – and not statistical – considerations, NYX-783 50 mg did achieve statistically significant improvements on some endpoints compared to placebo. In the study, NYX-783 demonstrated a favorable tolerability profile with no drug-related serious adverse events reported. Overall the adverse event profile was similar to that observed with placebo and the adverse events that were observed with NYX-783 were mild to moderate in nature. As this study was the first evaluation of NYX-783 in patients with PTSD, and given its exploratory nature, the p-values described are not adjusted for multiple comparisons as is typical with studies of this stage and nature.

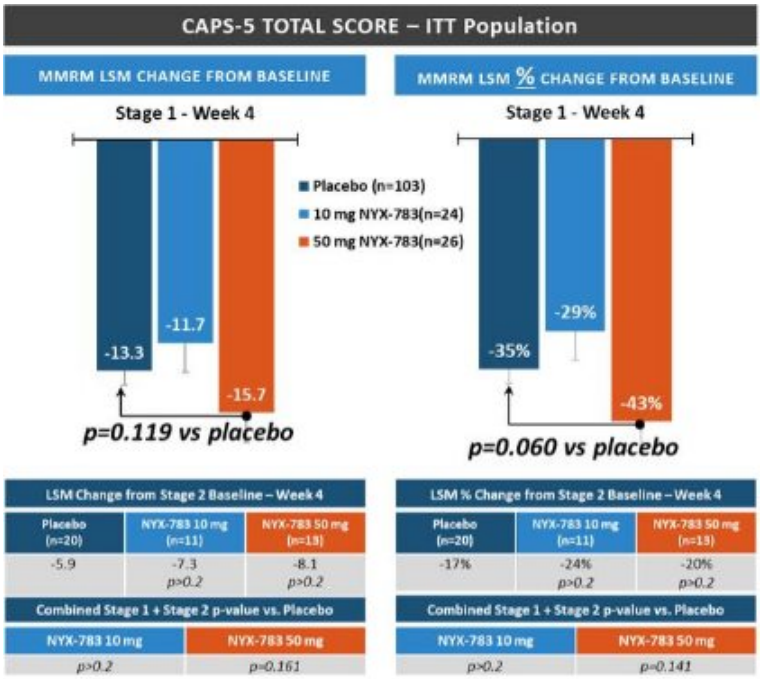
The table below illustrates the key endpoints from the study, demonstrating activity with the 50 mg dose across a number of endpoints. In particular, these effects were evident in Stage 1 of the study, which is most consistent with the design of our anticipated next study (i.e., a standard, placebo-controlled, randomized, parallel-design). Further, while the sequential parallel comparison design employed in this study was intended to mitigate the anticipated high placebo effects often observed in psychiatric studies, certain factors contributed to making the Stage 2 data more difficult to interpret and, ultimately, less informative for future studies. Most notably, a relatively high placebo response rate was observed in Stage 1, leading to fewer subjects in the placebo non-responder group in Stage 2. Thus, we have primarily relied upon the data from Stage 1 for interpretation of the signal observed in the study and for informing the design of the next study.

	Stage 1 (4 weeks) ITT Population			Stage 2 (4 weeks) ITT - PBO Non-Responders			Combined Stage 1 + Stage 2 p-value vs. Placebo	
	MMRM LSM (SE) Change from Baseline Randomized, Parallel Design Portion			MMRM LSM (SE) Change from New Baseline Following 4 Weeks of Placebo in Stage 1				
	Placebo	NYX-783 50 mg	NYX-783 10 mg	Placebo	NYX-783 50 mg	NYX-783 10 mg	NYX-783 50 mg	NYX-783 10 mg
	N=103	N=26	N=24	N=20	N=15	N=11		
Primary Efficacy Endpoints (MMRM LSM (SE))								
CAPS-5 Total *p-value vs. placebo*	-13.3 (0.84)	-15.7 (1.79) *p=0.1194*	-11.7 (1.74) *p>0.2*	-5.9 (1.78)	-7.3 (2.24) *p>0.2*	-8.1 (2.29) *p>0.2*	*p=0.1611*	*p>0.2*
CAPS-5: Arousal & Reactivity *p-value vs. placebo*	-2.7 (0.23)	-4.2 (0.48) *p=0.0043*	-3.5 (0.47) *p=0.0646*	-1.0 (0.55)	-2.0 (0.69) *p=0.1307*	-2.6 (0.68) *p=0.0373*	*p=0.0392*	*p=0.0499*
CAPS-5: Negative Cognitions & Mood *p-value vs. placebo*	-4.2 (0.40)	-5.7 (0.84) *p=0.0485*	-3.4 (0.82) *p>0.2*	-1.9 (0.75)	-2.0 (0.94) *p>0.2*	-2.1 (0.97) *p>0.2*	*p=0.1382*	*p>0.2*
CAPS-5: Intrusion *p-value vs. placebo*	-4.4 (0.28)	-4.2 (0.60) *p>0.2*	-3.7 (0.57) *p>0.2*	-2.3 (0.68)	-2.8 (0.83) *p>0.2*	-2.3 (0.83) *p>0.2*	*p>0.2*	*p>0.2*
CAPS-5: Avoidance *p-value vs. placebo*	-1.8 (0.17)	-2.2 (0.35) *p=0.1430*	-1.4 (0.35) *p>0.2*	-0.8 (0.34)	-0.6 (0.42) *p>0.2*	-1.6 (0.42) *p=0.0614*	*p>0.2*	*p>0.2*
Secondary Efficacy Endpoints (MMRM LSM (SE))								
PCL-5 *p-value vs. placebo*	-16.4 (1.14)	-19.9 (2.46) *p=0.0987*	-16.3 (2.36) *p>0.2*	-5.1 (1.96)	-5.7 (2.44) *p>0.2*	-8.6 (2.48) *p=0.1378*	*p=0.1703*	*p>0.2*
HADS-Anxiety *p-value vs. placebo*	-3.1 (0.27)	-4.4 (0.57) *p=0.0183*	-4.3 (0.56) *p=0.0239*	-1.0 (0.58)	-0.6 (0.72) *p>0.2*	-2.4 (0.72) *p=0.0672*	*p=0.1659*	*p=0.0450*
CGI-S *p-value vs. placebo*	-1.1 (0.08)	-1.2 (0.17) *p=0.1752*	-1.2 (0.16) *p>0.2*	-0.6 (0.18)	-0.7 (0.22) *p>0.2*	-0.8 (0.22) *p>0.2*	*p>0.2*	*p>0.2*

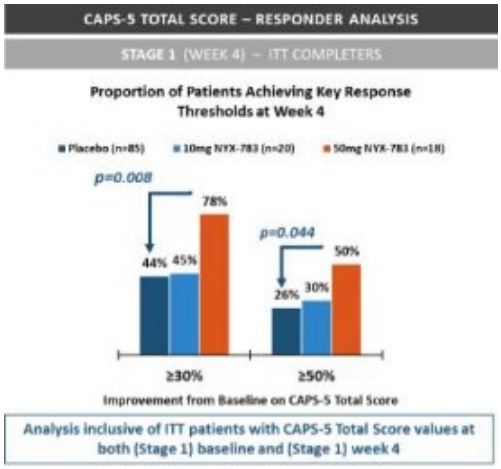
Endpoints in this exploratory study assessed with pre-specified one-sided α of p<0.1, LSM calculated using MMRM

p<0.05 vs. placebo | p<0.1 vs. placebo

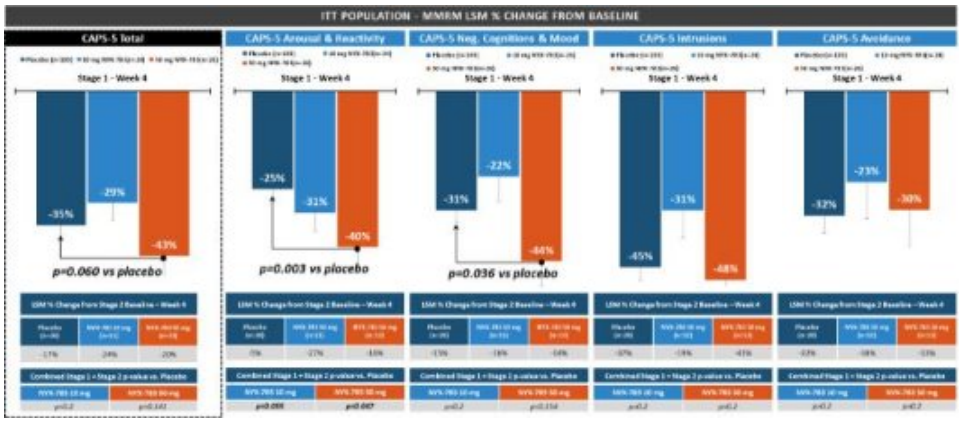
The graphs below demonstrate the signals observed on the CAPS-5 Total score. The 15.7-point improvement observed with the 50 mg dose (left panel) reflects a clinically meaningful improvement from baseline in four weeks. We believe it provides evidence of the potential for NYX-783 to significantly outperform placebo in a longer, well-powered study with greater emphasis on operational measures to mitigate placebo effects and variability. Percentage changes from baseline are also depicted (right panel), controlling for the slight imbalances in the baseline values that were observed across groups. Though this study was powered based on clinical considerations, and not statistical considerations, the percentage improvement from baseline was significantly greater for the NYX-783 50 mg group than placebo (using the pre-specified one-sided α of 0.1, reflective of the exploratory nature of the study).



The percentage of patients receiving NYX-783 who achieved meaningful response thresholds on the CAPS-5 Total score also points to the compound's potential to offer symptomatic relief across a broad array of patients. In this study, a 50 mg dose of NYX-783 demonstrated a statistically significantly greater response rate than placebo. The graph below shows the response rates observed at key response thresholds (≥ 30% improvement and ≥ 50% improvement). We believe these response rates further support the potential for NYX-783 to exhibit significant improvements on the CAPS-5 Total score in a longer, well-powered study.



The CAPS-5 comprises four symptom clusters that were also evaluated separately as part of the pre-specified primary analysis in the study. In the Phase 2 exploratory study in PTSD patients, NYX-783 exhibited robust reductions from baseline (> 40%) across three of the four symptom clusters, with the greatest separation from placebo observed on the Arousal & Reactivity and Negative Cognitions & Mood clusters. We believe the consistency of the improvements observed across the clusters provides further support for the strength of the overall signal with NYX-783. The effects observed across all four symptoms clusters are summarized below.



We believe the totality of the data observed in this study support the continued development of NYX-783 for the treatment of PTSD. To validate the findings from this initial exploratory study, following interaction with FDA to obtain guidance on the required parameters for a registration study, we expect to initiate a follow-up Phase 2b study of NYX-783 with a design consistent with those requirements.

Future Development

We intend to advance NYX-783 toward regulatory approval for the treatment of PTSD. In addition, we may pursue other neuropsychiatric indications for NYX-783, potentially including substance use disorders in which the enhancement of extinction learning processes observed with NYX-783 may offer therapeutic benefits.

In addition to pursing FDA approval in the United States in these indications, we also plan to explore registrations outside of the United States in the most significant markets, including but not limited to the European Union, Japan, Canada, Australia, and large emerging markets such as China.

NYX-458 for the Treatment of Cognitive Impairment

NYX-458 is a novel, oral, small-molecule NMDAr modulator in Phase 2 clinical development for the treatment of cognitive impairment associated with Parkinson's disease or dementia with Lewy bodies. Mechanistic rationale and compelling preclinical data in numerous models of cognitive impairment suggest NYX-458 may be suited to treat cognitive deficits associated with Parkinson's disease and dementia with Lewy bodies. Following the successful completion of a Phase 1 safety study in healthy volunteers, in December 2019 we initiated an exploratory Phase 2 study in patients with cognitive impairment associated with Parkinson's disease. Due to challenges introduced by the COVID-19 pandemic, in March 2020 we suspended enrollment of new patients in this study. In recent months, we have resumed site activation and we anticipate the imminent resumption of screening and enrollment of patients in this study.

In April 2019, we reported the results of a Phase 1 safety and pharmacokinetic study of NYX-458. In the randomized, placebo-controlled study, which included 62 healthy volunteers, single and multiple ascending oral doses of NYX-458 were evaluated across a 20-fold dose range—10 mg to 200 mg. Across the study, including in a cohort of elderly volunteers, NYX-458 demonstrated a favorable tolerability profile with no serious adverse events reported and no

adverse events leading to discontinuation. Only two adverse events in the study—one headache and one case of nausea—were considered possibly related to NYX-458 and both were characterized as mild.

Further, NYX-458 demonstrated a dose-proportional pharmacokinetic profile and no meaningful accumulation was observed with seven daily doses. We believe the highly predictable nature of this pharmacokinetic profile enables accurate dose selection to achieve appropriate therapeutic exposure in clinical development. As evaluated through cerebral spinal fluid drug concentration, NYX-458 demonstrated CNS exposure in line with that observed at preclinically active doses. CSF exposure levels were approximately 15% of the plasma concentration, similar to observations in preclinical studies.

Prevalence and Market Opportunity

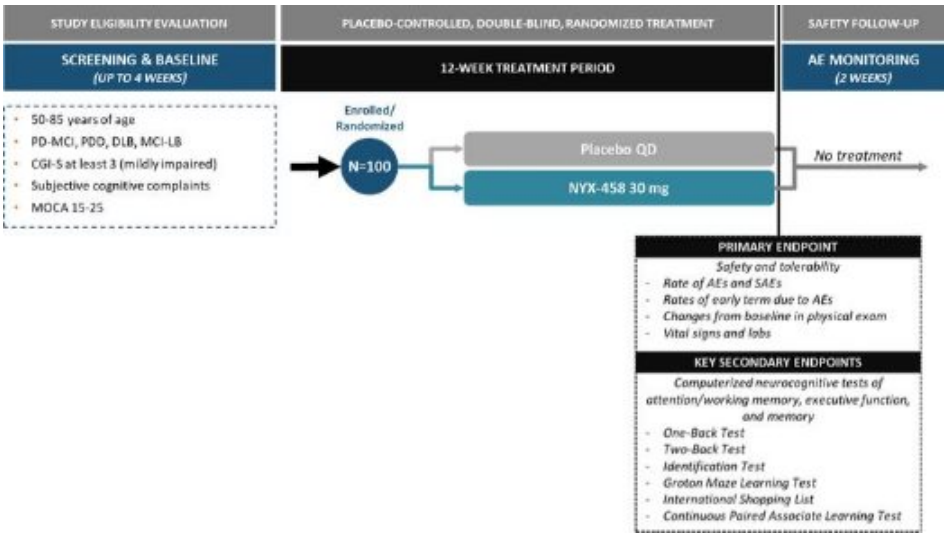
Parkinson's disease is believed to be the second most common neurodegenerative disorder, behind Alzheimer's disease. According to the Parkinson's Foundation, Parkinson's disease affects approximately one million people in the United States and nearly ten million worldwide. It is estimated that there are nearly 60,000 new cases of Parkinson's disease diagnosed annually in the United States and, as the population continues to age, it is anticipated that the prevalence of Parkinson's disease will continue to grow. The emergence and progression of cognition-related symptoms in Parkinson's disease can vary due to the diverse underlying pathology of the disease; however, mild cognitive impairment, or MCI, is an early non-motor symptom and affects 15% to 25% of newly diagnosed patients. It is estimated that approximately 30% of people living with Parkinson's disease have Parkinson's disease dementia, or PDD, and studies estimate that, as people with Parkinson's disease approach ten years post-diagnosis, 75% will have PDD. Based on these percentages, we estimate there are more than 500,000 people in the United States with either Parkinson's disease with mild cognitive impairment or PDD.

Lewy body dementia (LBD) is a type of progressive dementia that leads to a decline in thinking, reasoning and independent function because of abnormal microscopic deposits that damage brain cells over time. It is estimated that LBD is the third most common cause of dementia – accounting for 5 to 10 percent of cases in the U.S.

LBD and Parkinson's have been shown to share a common pathology – both believed to be caused by the build up of alpha-synuclein in the brain. Studies have shown that these increases in alpha-synuclein inhibt NMDA receptor activity, leading to decreased cognitive performance. We believe that, if approved, NYX-458 has the potential to improve the cognitive performance of these patience through enhancing NMDA receptor activity.

Phase 2 Clinical Study Currently in Progress

Following the suspension of enrollment in the previously initiated exploratory study of NYX-458 in patients with Parkinson's cognitive impairment, we have made certain adjustments to the study to simplify its design and to evaluate NYX-458 in a broader patient population that shares a common underlying pathophysiology with that of people with Parkinson's disease. In recent months we have recommenced study activities, including site activitations and protocol approvals by the Investigational Review Board, and we expect to begin screening and enrolling patients immediately following an investigator meeting scheduled for March 26, 2021. The amended study design is depicted below.



Non-human primate model of Parkinson's Disease Cognitive Impairment

We have evaluated NYX-458 in a non-human primate model of Parkinson's disease cognitive impairment. This model is relevant and translatable, as it evaluates the product candidate's effects in non-human primates by employing the neurotoxin MPTP to deplete dopamine-producing neuronal cells (similar to the way Parkinson's disease does in humans) and measuring cognitive function using the same battery of tests used in human clinical studies. In a study using this model, oral administration of NYX-458 resulted in a reversal of MPTP-induced cognitive impairment and, on some measures, restored cognitive function back to pre-MPTP healthy baseline levels.

Future development

We intend to develop NYX-458 toward regulatory approval for the treatment of Parkinson's disease cognitive impairment and dementia with Lewy bodies.

We believe the mechanism of NYX-458 may be effective across cognitive impairment due to varying etiologies. Based on the results seen in preclinical studies and on the effects to be observed in patients in the Phase 2 study currently in progress, we may seek to expand clinical development to other diseases associated with cognitive impairment.

Competition

Overview

Our industry is highly competitive and subject to rapid and significant technological change. The large and growing markets for pain, PTSD, Parkinson's disease, and other disorders of the brain and nervous system make them attractive therapeutic areas for biopharmaceutical businesses. While we believe that our employees and consultants, scientific knowledge, technology, and development experience provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies, academic institutions, governmental agencies, and public and private research institutions. Several of these entities have commercial products, robust drug pipelines, readily available capital, and established research and development organizations. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical studies, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and diagnostic industries may result in even more resources being

concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Small 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 all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of branded and generic competition, and the availability of reimbursement from government and other third-party payors.

NMDAr-targeted therapies

A number of pharmaceutical, biotechnology, and specialty pharmaceutical companies are developing therapies targeting NMDArs. Most of the therapies being developed are broad antagonists and tend to have multiple target actions while our compounds are truly modulatory and have not demonstrated any off-target activity in preclinical screening. We are aware of other companies developing or commercializing NMDAr-targeted therapies, including but not limited to, Acadia Pharmaceuticals Inc., Adamas Pharmaceuticals Inc., Allergan plc (now a subsidiary of AbbVie), Avanir Pharmaceuticals, Inc., Axsome Therapeutics, Inc., Biohaven Pharmaceutical Holding Co. Ltd., Cadent Therapeutics, Inc., Cerecor Inc., Eli Lilly and Company, Genentech Inc., Intra-Cellular Therapies, Inc., Janssen Pharmaceuticals, Inc., NeuroRx, Inc., Newron Pharmaceuticals S.p.A., Otonomy, Inc., Relmada Therapeutics, Inc., Sage Therapeutics, Inc., UCB S.A., Gate Neurosciences, Inc., and Vistagen Therapeutics, Inc.

NYX-2925—neuropathic/chronic pain

We expect that, if approved, NYX-2925 will compete with the currently approved therapies for painful DPN and fibromyalgia, including pregabalin, duloxetine, and tapentadol HCl. We are aware of a number of therapies that are approved to treat other types of neuropathic pain. We are also aware that various therapies are used off-label to treat neuropathic pain. In addition to the marketed therapies, we are aware of companies currently developing therapies for neuropathic pain, including Arbor Pharmaceuticals LLC, AstraZeneca Plc., Biogen Inc., Cara Therapeutics, Inc., Daiichi Sankyo Company, Eli Lilly and Company, GW Pharmaceuticals plc., Immune Pharmaceuticals Inc., NeuroBo Pharmaceuticals, Novaremed AG, Novartis AG, Vertex Pharmaceuticals Incorporated, and ViroMed Inc.

NYX-783—post-traumatic stress disorder

We expect that, if approved, NYX-783 will compete with currently approved therapies for PTSD, including paroxetine and sertraline. We are also aware of other companies developing therapies for PTSD, including but not limited to, Azevan Pharmaceuticals Inc., Bionomics Ltd., Otsuka Pharmaceutical Co., Ltd., SpringWorks Therapeutics, and Tonix Pharmaceuticals Holding Corp.

NYX-458—Parkinson's disease cognitive impairment and dementia with Lewy bodies

We expect that, if approved, NYX-458 will compete with currently approved therapies for PDD, the only one of which in the United States is rivastigmine. We are also aware of other companies developing therapies for Parkinson's disease cognitive impairment, including but not limited to, Anavex Life Sciences, Annovis Bio Inc, Eli Lilly and Company, Sage Therapeutics Inc, Takeda Pharmaceutical Co Ltd, and Eisai Pharmaceuticals Inc.

Research collaboration agreement with Allergan

The jointly funded research activities and option exercise period under our Research Collaboration Agreement, or RCA, with Allergan (now a subsidiary of AbbVie) came to their contractual conclusion in August 2020 and February 2021, respectively. Consistent with the terms of the RCA, AbbVie has optioned two compounds from our NMDAr modulator discovery platform.

Overview

In July 2015, we entered into an RCA with Allergan, pursuant to which we and Allergan have research, development, and commercial rights to compounds discovered using our discovery platform. The research collaboration was structured to afford Allergan an option to obtain field-limited rights for up to three of the compounds discovered under the research collaboration. In exchange for these rights, Allergan reimbursed us for a certain percentage of the direct costs associated with the medicinal chemistry, screening, and profiling efforts conducted as part of the research collaboration. Allergan also paid us a fixed annual rate per full time employee, or FTE, for each individual assigned to these discovery efforts.

During the term of the RCA, Allergan could exercise up to three options to acquire full rights (including field-limited development and commercialization rights) for compounds from our discovery platform. Allergan research, development, and commercialization on optioned compounds is limited to a field of specified indications, including Alzheimer's disease, delirium, and a list of psychiatric disorders (which list does not include PTSD or substance use disorder). By their terms, these field-related restrictions pertaining to Allergan's license rights survive the expiration of the Agreement and the exclusivity period.

Under this agreement, each time Allergan exercised an option, it was required to pay us an option exercise fee of $1.0 million and we were required to (a) assign to Allergan rights in intellectual property that pertains only to the Allergan-optioned compound if possible, and (b) grant Allergan a fully-paid, perpetual, exclusive (including with regard to Aptinyx) and irrevocable license under other intellectual property we control that pertains to both the optioned compound and also pertains to other compounds or uses, solely to develop and commercialize the optioned compound within Allergan's field of specified indications. On May 16, 2018, Allergan exercised its option to acquire the compound designated AGN-241751, triggering payment of a $1.0 million option fee in connection with such exercise. On February 23, 2021, Allergan exercised its option to acquire the compound designated AGN-281705, triggering payment of a $1.0 million option fee in connection with such exercise. We will receive no further economic consideration from these product candidates. As the period of jointly funded research and option exercise period under this agreement have now reached their contractual conclusions, Allergan has no additional option exercise rights.

We may research and develop any of our compounds as therapies for any indication outside of Allergan's field of specified indications. We have invented, and therefore own, most intellectual property pertaining to compounds from our discovery platform, but Allergan must grant us a non-exclusive license under any intellectual property rights Allergan may own related to our compounds to develop and commercialize compounds outside of Allergan's field of specified indications.

During the exclusivity period set forth in the agreement (which period expires on the third anniversary of the end of the RCA term), we have agreed not to, alone or with a third party, directly or indirectly, engage in the research, preclinical development, clinical development, or commercialization of any compound or any product for the purpose of the treatment, prevention or diagnosis of any disorders or conditions in Allergan's field of specified indications. In addition, any chemistry or technology we discover or develop related to the modulation of NMDArs for therapeutic effect is and will be subject to the terms of the agreement, including any exclusive license granted to Allergan in Allergan's field of specified indications. Under the terms of the license granted under the RCA, for a period that extends beyond the expiration of the RCA term and the exclusivity period, Allergan and its affiliates will not have the right to, alone or with a third party, directly or indirectly, engage in the research, preclinical development, clinical development, or commercialization of the compounds it acquires under the research collaboration for the purpose of the treatment, prevention, or diagnosis of any disorders or conditions outside Allergan's field of specified indications, without first obtaining our approval at our sole discretion.

The term of the RCA expired on the expiration of Allergan's option period on February 24, 2021, subject to the completion of all post-option transfer activities.

This collaboration has enabled both parties to advance compounds from our discovery platform into clinical studies.

Manufacturing

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacturing of our product candidates for preclinical and clinical testing, as well as for commercial manufacturing if our product candidates receive marketing approval.

As a key part of our product development approach, we aim to complete formulation work at an early stage of development, such that our clinical studies are conducted with a formulation that has the potential for eventual scale-up.

All of our product candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry does not require unusual equipment in the manufacturing process, although certain manufacturers may choose to manufacture our product candidates in specifically isolated facilities since many are spiro-beta lactams. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Commercialization

We intend to develop and, if approved by the FDA, to commercialize our product candidates in the United States. We may work in combination with one or more large pharmaceutical partners for certain indications. Depending on the specific development path pursued, this may include larger chronic pain indications. For other, more specialized indications, we intend to commercialize our product candidates independently. For example, we believe the patient and prescriber populations for Parkinson's disease cognitive impairment are relatively concentrated and can be addressed with a focused sales team of fewer than 200 full-time employees. We also do not believe any existing pharmaceutical companies have significant expertise in the commercialization of therapies in this specific area. We will, however, continuously review our partnering strategy in the light of new clinical data and market understanding. We may enter into distribution or licensing arrangements for commercialization rights for other regions outside the United States.

Intellectual property

Our owned patents and patent applications relate to our NMDAr modulating compounds and include patents and patent applications directed to new compositions of matter and to methods of treating brain and nervous system disorders. We intend to seek patent protection in the United States and in selected jurisdictions worldwide.

NYX-2925 and NYX-783

As of February 15, 2021, we own two issued U.S. patents, and pending and issued foreign counterpart patents and patent applications, that relate to both NYX-2925 and NYX-783. We also own one issued U.S. patent and two pending U.S. patent applications that relate to NYX-2925, and one issued U.S. patent, one pending U.S. patent application and one pending U.S. provisional patent application that relate to NYX-783. A provisional patent application is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of filing of the provisional patent application. The issued U.S. patents are expected to expire in 2034. If we continue to pursue patent protection and file a non-provisional patent application with respect to our provisional patent application, and if any patents issue based on our pending applications, we expect such patents, if issued, to expire between 2034 and 2041.

NYX-458

As of February 15, 2021, we own one issued U.S. patent, three pending U.S. patent applications, and one pending U.S. provisional patent application, and pending foreign counterpart patent applications, as well as one pending international

patent application filed under the Patent Cooperation Treaty (PCT) that relate to our product candidate, NYX-458. An international PCT patent application is not eligible to become an issued patent until, among other things, we file a patent application in regional or national patent offices within 30 or 31 months of filing of the earliest-filed priority patent application. The issued U.S. patent is expected to expire in 2037. If we continue to pursue patent protection and file one or more patent applications with respect to our pending international PCT patent application, and if any patents issue based on our pending applications, we expect such patents, if issued, to expire between 2037 and 2040.

Other compounds

As of February 15, 2021, we own thirteen issued U.S. patents, seven pending U.S. patent applications, and pending and issued foreign counterpart patents and patent applications, as well as nine U.S. provisional patent applications, all of which generally relate to our efforts to develop other compounds in our NMDAr modulator small molecule program. Provisional patent applications are not eligible to become issued patents until, among other things, we file a non-provisional patent application within 12 months of filing the provisional patent applications. The issued U.S. patents are expected to expire between 2034 and 2037. If we continue to pursue patent protection and file one or more non-provisional patent applications with respect to our pending provisional patent applications, and if any patents issue based on our pending applications, we expect such patents, if issued, to expire between 2034 and 2041. For a discussion of the risks associated with our intellectual property, see "Risk Factors —Risks related to our intellectual property rights."

Government regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. drug development

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and its implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Additionally, a manufacturer may need to recall a product from the market. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of extensive nonclinical laboratory tests, animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND application, which must become effective before human clinical studies may begin;
- approval by an independent institutional review board, or IRB, or ethics committee at each clinical study site before each study may be initiated;

- performance of adequate and well-controlled human clinical studies in accordance with applicable IND and other clinical study-related regulations, referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for each proposed indication;
- submission to the FDA of an NDA for a new drug;
- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- potential FDA audit of the nonclinical study and/or clinical study sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the drug in the United States.

The nonclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

The data required to support an NDA is generated in two distinct development stages: nonclinical and clinical. For new chemical entities, the nonclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. These nonclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the nonclinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. Some nonclinical testing may continue even after the IND is submitted, but an IND must become effective before human clinical studies may begin. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical studies, including concerns that human research subjects will be exposed to unreasonable health risks, and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical studies due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that could cause the study to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical study must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical study

subject or his or her legal representative and must monitor the clinical study until completion. There are also requirements governing the reporting of ongoing clinical studies and completed clinical study results to public registries.

As part of the 21st Century Cures Act, or the Cures Act, which was signed into law on December 13, 2016, upon request, the FDA is to establish a process for the qualification of drug development tools. A drug development tool includes a biomarker including a surrogate endpoint, a clinical outcome assessment including a patient-reported outcome, and any other method, material or measure that the FDA determines aids drug development and regulatory review. A drug development tool is qualified if the FDA has determined that the tool and its proposed context of use can be relied upon to have a specific interpretation and application in drug development and regulatory review. A qualified drug development tool may be used to support the investigational use of a drug or support or obtain NDA approval.

A sponsor who wishes to conduct a clinical study outside the United States may, but need not, obtain FDA authorization to conduct the clinical study under an IND. If a foreign clinical study is not conducted under an IND, the sponsor may submit data from the clinical study to the FDA in support of an NDA so long as the clinical study is conducted in compliance with GCP and the FDA is able to validate the data through an onsite inspection if the agency deems it necessary.

Clinical studies

Clinical studies are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2, and Phase 3 clinical studies.

- Phase 1 clinical studies generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical studies is to assess the metabolism, pharmacologic action, side effect tolerability, and safety of the drug.

- Phase 2 clinical studies typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits and provide a preliminary evaluation of efficacy. At the same time, safety, and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks.

- Phase 3 clinical studies generally involve large numbers of patients at multiple sites (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use and its safety in use, to establish the overall benefit/risk relationship of the product, and to provide an adequate basis for physician labeling. Phase 3 clinical studies may include comparisons with placebo and/or comparator treatments.

Post-approval studies, sometimes referred to as Phase 4 clinical studies, may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical studies as a condition of approval of an NDA.

Progress reports detailing the results of the clinical studies must be submitted at least annually to the FDA. Written IND safety reports must be submitted to the FDA and the investigators within 15 calendar days for serious and unexpected suspected adverse events, finding from other studies or animal or *in vitro* testing that suggests a significant risk for human subjects, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Additionally, a sponsor must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days. Phase 1, Phase 2, and Phase 3 clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical studies are overseen by an

independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study.

Pursuant to the Cures Act, the manufacturer of an investigational drug for a serious disease or condition is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for individual patient access to such investigational drug. This requirement applies on the earlier of the first initiation of a Phase 2 or Phase 3 study of the investigational drug, or as applicable, 15 days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy.

Concurrently with clinical studies, companies usually 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 sponsor must develop methods for testing the identity, strength, quality, and purity of the final drug product. 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.

NDA and FDA review process

The results of the nonclinical studies and clinical studies, together with other detailed information, including extensive manufacturing information and information on the composition of the drug and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality, and purity. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

In addition, under the Pediatric Research Equity Act, or PREA, as amended, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective from October 1, 2020 through September 30, 2021, the user fee for an application requiring clinical data, such as an NDA, is $2,875,842. PDUFA also imposes an annual prescription drug product program fee for human drugs ($336,432). Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, for drugs that do not contain an NCE, the FDA has 10 months from the receipt date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the receipt date for a priority NDA. For drugs containing an NCE, these ten- and six-month review timeframes are from the filing date of an NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product 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, before approving an NDA, the FDA may also audit data from clinical studies to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and 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. The FDA will likely re-analyze the clinical study data, which could result in extensive discussions between the FDA and the applicant during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

After the FDA evaluates an NDA, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical study(s), and/or other significant and time-consuming requirements related to clinical studies, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, or request an opportunity for a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings, or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing or clinical studies and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical studies designed to further assess a drug's safety and efficacy and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA also may place other conditions on approvals including the requirement for a risk evaluation and mitigation strategy, or REMS, to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product available in the United States for this type of disease or condition will be recovered from sales of the product.

Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not

approve any other applications to market the same drug for the same indication for seven years from the date of such approval, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care, or in instances of drug supply issues. Competitors, however, may receive approval of either a different product for the same indication or the same product for a different indication but that could be used off-label in the orphan indication. Orphan drug exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval before we do for the same product, as defined by the FDA, for the same indication we are seeking approval, or if our product is determined to be contained within the scope of the competitor's product for the same indication or disease. If one of our products designated as an orphan drug receives marketing approval for an indication broader than that which is designated, it may not be entitled to orphan drug exclusivity. Orphan drug status in the European Union has similar, but not identical, requirements and benefits.

Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug may request the FDA to designate the drug as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may review sections of the marketing application on a rolling basis before the complete NDA is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under the Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review. A product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or offers a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review.

Additionally, a drug may be eligible for designation as a breakthrough therapy if the drug 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 existing therapies on one or more clinical development. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus intensive guidance from FDA to ensure an efficient drug development program. Fast Track designation, priority review, and breakthrough designation do not change the standards for approval but may expedite the development or approval process.

Pediatric trials

The FDCA requires that a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical studies and/or other clinical development programs.

Post-marketing requirements

Following approval of a new product, a pharmaceutical company and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the FDA of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional nonclinical studies and clinical studies. As with new NDAs, the review process is often significantly extended by FDA's requests for additional information or clarification. Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These manufacturers must comply with cGMP regulations that require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. The discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market.

Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development. Changes in statutes, regulations, or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

Orange Book listing

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 Section 505(b)(2) NDA is an application in which the applicant, in part, relies on 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. 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. Limited changes must be preapproved by the FDA via a suitability petition. ANDAs are termed "abbreviated" because they are generally not required to include nonclinical and clinical 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.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents having claims that cover the applicant's product and method of use. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book. These products may be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA.

Any applicant who files an ANDA seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must make patent certifications to the FDA that (1) no patent information on the drug or method of use that is the subject of the application has been submitted to the FDA; (2) the patent has expired; (3) the date on which the patent will expire and approval will not be sought until after the patent expiration; or (4) the patent is invalid or will not be infringed upon by the manufacture, use, or sale of the drug product for which the application is submitted. The last certification is known as a paragraph IV certification. 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 a paragraph IV certification or if the applicant is not seeking approval of a patented method of use. If the applicant does not challenge the listed patents or does not indicate 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 competitor has provided a paragraph IV certification to the FDA, the competitor must also send notice of the paragraph IV certification to the holder of the NDA for the reference listed drug and the patent owner within 20 days after the application has been accepted for filing by the FDA. The NDA holder or patent owner may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a paragraph IV certification notice prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of 30 months from the date of the lawsuit, expiration of the patent, settlement of the lawsuit, a decision in the infringement case that is favorable to the applicant 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 owners 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.

U.S. marketing exclusivity

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving abbreviated new drug applications, or ANDAs, for drugs containing the active agent for the original indication or condition of use. The FDCA also provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant

to obtain approval of an NDA for an NCE. A drug is an NCE if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. While we believe there is a likelihood that the FDA would grant NCE status to both NYX-2925 and NYX-783 if both are granted regulatory approval, NYX-2925 and NYX-783 have the same structural formula but differ in spatial orientation, i.e., are separate stereoisomers of each other, and there can be no assurance that both will be granted NCE exclusivity. Three-year and five-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical studies necessary to demonstrate safety and efficacy. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

U.S. patent-term extension

Depending upon the timing, duration and specifics of FDA approval of our current product candidates or any future product candidate, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch Waxman Act. The Hatch Waxman Act permits extension of the patent term of up to five years as compensation for patent term lost during FDA regulatory review process. Patent term extension, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term extension period is generally 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 approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved drug is eligible for the extension (and only those patient claims covering the approved drug, a method for using it or a method for manufacturing it may be extended), and the application for the extension must be submitted prior to the expiration of the patent. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension. In the future, we may apply for extension of patent term for our currently owned patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant NDA. However, there can be no assurance that the USPTO will grant us any requested patent term extension, either for the length we request or at all.

Other regulatory matters

Manufacturing, sales, promotion, and other activities following product approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, CMS, other divisions of the Department of Health and Human Services including the Office of the Inspector General, the U.S. Department of Justice, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local regulatory authorities. In the United States, sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. These laws include the federal Anti-Kickback Statute, which makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchase, order, or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison (per violation), criminal fines, administrative civil money penalties and exclusion from participation in federal healthcare programs. In addition, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute. A

person or entity does not need to have actual knowledge of the statute or specific intent to violate it. Moreover, the ACA provides that 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.

Although we would not submit claims directly to payors, drug manufacturers can be held liable under the federal civil False Claims Act, which prohibits anyone from knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. The government may deem manufacturers to have "caused" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for a False Claims Act violation include civil penalties for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the federal False Claims Act and certain states have enacted laws modeled after the federal False Claims Act.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors. It also prohibits willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Like the federal Anti-Kickback Statute a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The civil monetary penalties statute imposes penalties against any person or entity that, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. Also, many states have similar fraud and abuse statutes or regulations that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, to the extent that any of our product candidates, if approved, are sold in a foreign country, we may be subject to similar foreign laws.

We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, including the final omnibus rule published on January 25, 2013, mandates, among other things, the adoption of uniform standards for the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy and security of individually identifiable health information, which require the adoption of administrative, physical and technical safeguards to protect such information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, defined as independent contractors or agents of covered entities, which include certain health care providers, health plans, and healthcare clearinghouses, that create, receive, maintain, transmit, or obtain protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities and 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 attorney's fees and costs associated with pursuing federal civil actions. In addition, certain state laws govern the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and criminal penalties.

Additionally, the federal Physician Payments Sunshine Act, or the Sunshine Act, within the Affordable Care Act, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to CMS information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. In addition, many states also govern the reporting of payments or other transfers of value, many of which differ from each other in significant ways, are often not pre-empted, and may have a more prohibitive effect than the Sunshine Act, thus further complicating compliance efforts.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Other regulations may affect other aspects of our business. For example, pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in ACA. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws. There has also been a recent trend of increased federal and state regulation of payments made to physicians. Certain states mandate implementation of compliance programs, impose restrictions on drug manufacturers' marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

Ensuring business arrangements with third parties comply with applicable healthcare laws and regulations is a costly endeavor. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

European Union drug development

In the European Union, our future products may also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the United States, the various phases of nonclinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical studies regulatory framework, setting out common rules for the control and authorization of clinical studies in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to

significant variations in the member state regimes. Under the current regime, before a clinical study can be initiated it must be approved in each of the EU countries where the study is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical study have to be reported to the NCA and ECs of the Member State where they occurred.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It is expected that the new Clinical Trials Regulation (EU) No 536/2014 will apply following confirmation of full functionality of the Clinical Trials Information System, the centralized European Union portal and database for clinical trials foreseen by the regulation, through an independent audit. The regulation becomes applicable six months after the European Commission publishes notice of this confirmation. It will overhaul the current system of approvals for clinical studies in the EU. Specifically, the new regulation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical studies in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single point and strictly defined deadlines for the assessment of clinical study applications.

European Union drug review and approval

In the United Kingdom and the European Economic Area, or EEA, comprising the 27 Member States of the European Union plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, and is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the Member States Concerned).

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

European Union new chemical entity exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. The data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator’s data to assess a generic application

for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven 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 determined to bring a significant clinical benefit in comparison with currently approved therapies.

European Union orphan designation and exclusivity

In the EU, the European Commission, based on the recommendation of the EMA's Committee for Orphan Medicinal Products, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU community (or where it is unlikely that the development of the medicine would generate sufficient return to justify the investment) and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or, if a method exists, the product would be a significant benefit to those affected).

In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period is extended by two years for compliance with an agreed upon pediatric investigation plan granted at the time of review of the orphan drug designation. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time, if (i) the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application, (ii) the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of the orphan medicinal product, or (iii) the second applicant can establish that the second medicinal product, although similar, is safer, more effective or otherwise clinically superior to the authorized orphan medicinal product. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

European data collection

The collection, use, storage, disclosure, transfer, or processing of personal data, including personal health data, in the EEA is governed by the General Data Protection Regulation 2016/679, or GDPR, which became effective May 25, 2018 and related applicable data protection and privacy laws of the member states of the EEA. The GDPR applies to any company established in the EEA and to companies established outside the EEA that process personal data in connection with the offering of goods or services to data subjects in the EEA or the monitoring of the behavior of data subjects in the EEA. The GDPR enhances data protection obligations for data controllers of personal data, including imposing special requirements in respect of the processing of health and other sensitive data (such as higher standards for data controllers to demonstrate that they have obtained valid consent for certain data processing activities, expanded disclosures about how personal data is used, requirements to conduct privacy impact assessments for "high risk" processing, limitations on retention of personal data, mandatory data breach notification and "privacy by design" requirements, safeguards to protect the security and confidentiality of personal data, and other measures to take when engaging third-party processors). EEA Member States may introduce further conditions, including limitations which could limit our ability to collect, use and share personal data (including health and medical information), or could cause our compliance costs to increase. The GDPR also imposes strict rules on the transfer of personal data outside of the EEA to countries that do not ensure an adequate level of protection, like the U.S. A recent decision of the Court of Justice of the European Union (CJEU) and related guidance issued by European data protection authorities require an "essential equivalency" assessment of the laws of the destination country. If essentially equivalent protections are not available in the destination country, the exporting entity must then assess if supplemental measures can be put in place that, in combination with the chosen transfer mechanism, would address the deficiency in the laws and ensure that essentially equivalent protection can be given to the data. This and other future developments regarding the flow of data across borders could increase the complexity of transferring personal data outside the EEA and may lead to governmental enforcement actions, litigation, fines and penalties or adverse publicity, which could have an adverse effect on our reputation and business.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EEA Member States may result in fines up to 20 million Euros or 4% of a company's global annual revenues for the preceding financial year, whichever is higher. The authorities have shown a willingness to impose significant fines and issue orders preventing the processing of personal data on non-compliant businesses. Moreover, the GDPR grants data subjects the right to claim material and non-material damages resulting from infringement of the GDPR and other European data protection laws. In addition to the foregoing, a breach of the GDPR or other applicable privacy and data protection laws and regulations could result in regulatory investigations, reputational damage, orders to change our use of data, enforcement notices, or potential civil claims including class action type litigation. Given the breadth and depth of data protection obligations, maintaining compliance with the GDPR will require significant time, resources and expense, and we will continue to face uncertainty as to whether our efforts to comply with our obligations under the GDPR will be sufficient. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

Brexit and the regulatory framework in the United Kingdom

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

Rest of the world regulation

For other countries outside of the European Union and the United States, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, pricing, and reimbursement vary from country to country. In all cases the clinical studies must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. In the United States no uniform policy of coverage and reimbursement for drug products exists. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor by payor basis. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved or that any required patient cost-sharing amount will be acceptable to the patient. Moreover, one payor's decision to cover a particular drug product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained.

Our ability to commercialize any products successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which therapeutics they will pay for and establish reimbursement levels. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a therapeutic is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

We cannot be sure that reimbursement will be available for any product that we commercialize and, if coverage and reimbursement are available, what the level of reimbursement will be. Coverage may also be more limited than the purposes for which the product is approved by the FDA or comparable foreign regulatory authorities. Reimbursement may impact the demand for, or the price of, any product for which we obtain regulatory approval.

Third-party payors are increasingly reducing reimbursements for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign 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 our net revenue and results. Decreases in third-party reimbursement for our products or a decision by a third-party payor to not cover our products could reduce physician usage of the products and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. 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 of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower.

Healthcare Reform

In the United States and some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system directed at broadening the availability of healthcare, improving the quality of healthcare, and containing or lowering the cost of healthcare.

For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA was enacted in the United States. The ACA includes measures that have significantly changed, and are expected to continue to significantly change, the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical industry are that the ACA:

- made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs to 23.1% of average manufacturer price, or AMP, and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP.
- imposed a requirement on manufacturers of branded drugs to provide a 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discount off the negotiated price of branded drugs dispensed to Medicare Part D beneficiaries in the coverage gap (i.e., "donut hole") as a condition for a manufacturer's outpatient drugs being covered under Medicare Part D.
- extended a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations.
- expanded the entities eligible for discounts under the 340B Drug Discount Program
- established 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.
- imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs, apportioned among these entities according to their market share in certain government healthcare programs.
- imposed new reporting requirements on drug manufacturers for payments made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers are required to submit reports to CMS by the 90th day of each calendar year.
- established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products. The ACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. Various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court; the former Trump Administration issued various Executive Orders which eliminated cost sharing subsidies; and Congress has introduced several pieces of

legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business, especially under the Biden administration.

The former Trump administration's budget proposal for fiscal year 2021 included a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the former Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Moreover, the former Trump administration also previously released a "Blueprint" that contained several potential regulatory actions and legislative recommendations aimed at lowering prescription drug prices, including measures to promote innovation and competition for biologics, changes to Medicare Part D to give plan sponsors more leverage when negotiating prices with manufacturers, and updating the Medicare drug-pricing dashboard to make price increases and generic competition more transparent. The U.S. Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option to use step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions after January 20, 2021.

In 2020, former President Trump announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021, and ending December 31, 2027. However, in response to a lawsuit filed by several industry groups, on December 28, the U.S. District Court for the Northern District of California issued a nationwide preliminary injunction enjoining government defendants from implementing the MFN Rule pending completion of notice-and-comment procedures under the Administrative Procedure Act. On January 13, 2021, in a separate lawsuit brought by industry groups in the U.S. District of Maryland, the government defendants entered a joint motion to stay litigation on the condition that the government would not appeal the preliminary injunction granted in the U.S. District Court for the Northern District of California and that performance for any final regulation stemming from the MFN Interim Final Rule shall not commence earlier than 60 days after publication of that regulation in the Federal Register. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the MFN Model may materially and adversely affect the price we receive for any of our product candidates. Additionally, on December 2, 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 an order entered by the U.S. District Court for the District of Columbia, the portion of the rule eliminating safe harbor protection for certain rebates related to the sale or purchase of a pharmaceutical product from a manufacturer to a plan sponsor under Medicare Part D has been delayed to January 1, 2023. Further, implementation of this change and new safe harbors for point-of-sale reductions in price for prescription pharmaceutical products and pharmacy benefit manager service fees are currently under review by the Biden administration and may be amended or repealed.

While many of the proposed measures will require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, Congress has indicated that it will continue to seek new legislative, administrative and/or additional measures to control drug costs.

Additionally, on October 1, 2020, FDA published a final rule that allows for the importation of certain prescription drugs from Canada. Under the final rule, States and Indian Tribes, and in certain future circumstances pharmacists and wholesalers, may submit importation program proposals to the FDA for review and authorization. Since the issuance of the final rule, several industry groups have filed federal lawsuits challenging multiple aspects of the final rule, and authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. 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. Separately, the FDA also issued a final guidance document outlining a pathway for manufacturers to obtain an additional National Drug Code, or NDC, for an FDA-approved drug that was originally intended to be marketed in a foreign country and that was authorized for sale in that foreign country. The market implications of the final rule and guidance are unknown at this time.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013, following passage of the Bipartisan Budget Act of 2013, and, due to subsequent legislative amendments, will remain in effect through 2029 unless additional congressional action is taken. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, also known as the CARES Act, as well as subsequent legislation, these reductions have been suspended from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic. Proposed legislation, if passed, would extend this suspension until the end of the pandemic. Further, in January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability. Additionally, 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 bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to request access to certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. 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.

We cannot predict what healthcare reform initiatives may be adopted in the future. Further federal, state and foreign legislative and regulatory developments are likely, and we expect ongoing initiatives to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates and may affect our overall financial condition and ability to develop product candidates.

Employees and Human Capital Management

As of March 15, 2021, we employed 34 full-time employees, including 20 in research and development and 14 in general and administrative, and no part-time employees. 9 of our employees hold M.D. or Ph.D. degrees. We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective-bargaining arrangements. We consider our relationship with our employees to be good.

Our human capital objectives include, as applicable, identifying, recruiting, retaining, incentivizing, and integrating existing and new employees, advisors, and consultants. Our success depends on our ability to attract, engage, and retain a diverse group of employees. We value our employees and regularly benchmark total rewards we provide, such as short and long term compensation, including stock-based compensation awards and payments of cash-based performance bonus awards, 401(k) contributions, health, welfare and quality of life benefits, paid time off and personal leave, against our industry peers to ensure we remain competitive and attractive to potential new hires. We also conduct employee engagement surveys to evaluate our success with respect to our human capital objectives and to allow us to retain and incentivize our existing employees. By focusing on employee retention and engagement, we improve our ability to support our clinical trials, our pipeline, and our business and operations, and also protect the long-term interests of our securityholders.

Our Corporate Information

We were incorporated under the laws of the state of Delaware in June 2015. Our principal executive offices are located at 909 Davis Street, Suite 600, Evanston, Illinois 60201. Our telephone number is (847) 871-0377, and our website is located at www.aptinyx.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, are available free of charge on our website located at www.aptinyx.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (the "SEC"). These reports are also available at the SEC's Internet website at www.sec.gov.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.aptinyx.com, under "Investors & Media".

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks and uncertainties, together with all other information in this Annual Report on Form 10-K, including our financial statements and related notes and "Management's Discussion and Analysis of Results of Operations and Financial Condition," as well as our other filings with the Securities and Exchange Commission, before investing in our common stock. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties actually occur, causing you to lose all or part of your investment in our common stock. The risks and uncertainties we describe below are not the only ones we face. Additional risks and uncertainties that we currently do not know about or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Special Note Regarding Forward-Looking Statements and Industry Data" in this Annual Report on Form 10-K.

Risks related to our business, financial position, and need for additional capital

We are a clinical-stage biopharmaceutical company with no products approved for commercial sale, which may make it difficult to evaluate our current business and predict our future success and viability.

We are a clinical-stage biopharmaceutical company focused on developing therapeutics for disorders of the brain and nervous system. We were incorporated in June 2015, have no products approved for commercial sale, and have not generated any revenue from product sales. Our operations to date have been limited primarily to organizing and staffing our company, raising capital, and conducting research and development activities for our product candidates.

We have not yet obtained marketing approval for any product candidates, manufactured a commercial scale product on our own or through a third party, or conducted sales and marketing activities necessary for successful product commercialization. Our future success and viability are subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer.

COVID-19 may materially and adversely affect our business and our financial results.

The continued spread of the COVID-19 pandemic declared by the World Health Organization in March 2020 has already and could further adversely impact our clinical and/or preclinical studies. For example, due to the COVID-19 pandemic, on March 27, 2020, we suspended the enrollment of new patients in our ongoing Phase 2 studies of NYX-2925 in painful DPN and fibromyalgia, which we resumed in January 2021 and September 2020, respectively, and in our Phase 2 study of NYX-458 in mild cognitive impairment associated with Parkinson's disease, which we have resumed certain activities for and expect to recommence screening and enrollment in the coming weeks. COVID-19 has resulted in disruptions in our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 if an outbreak occurs in their geography, and has delayed enrollment in our clinical studies due to prioritization of hospital resources toward the outbreak and restrictions in travel. Furthermore, some patients may be unwilling to enroll in our studies or be unable to comply with clinical study protocols if quarantines or travel restrictions impede patient movement or interrupt healthcare services. COVID-19 may also negatively affect the operations of third-party contract research organizations that we rely upon to carry out our clinical studies or the operations of our third-party manufacturers, which could result in delays or disruptions in the supply of our product candidates. The negative impacts COVID-19 has had to patient enrollment or treatment or the timing and execution of our clinical studies have caused and could cause further costly delays to our clinical study activities. For those clinical studies that currently remain ongoing, we cannot provide any assurances that the measures that we have taken to date, or may in the future take, will continue to allow us to mitigate and manage COVID-19-related disruptions, and COVID-19 may require us to delay or pause enrollment, dosing, or data collection in such studies as a result of negative impacts to site initiation, participant recruitment and enrollment, participant randomization and dosing, distribution of clinical study materials, study monitoring, or data analysis. Even if we are able to collect clinical data while the outbreak is ongoing, COVID-19 may negatively affect the quality, completeness, integrity, and interpretability of such clinical data as a result of deviations from clinical study protocols, disruptions in patient screening or dosing (for instance, as a result of inabilities to supply study drug direct-to-patients via delivery or courier), or disruptions in patient evaluations (for instance, as a result of inabilities to conduct study visits while following local public health requirements or inabilities to conduct remote assessments). Any of these effects could adversely affect our ability to advance our product candidates in the manner and on the timelines presently planned, obtain regulatory approval for and to commercialize our product candidates, increase our operating expenses, and have a material adverse effect on our business and financial results.

In addition, COVID-19 has resulted in significant governmental measures being implemented to control the spread of the virus, including quarantines, travel restrictions, and business shutdowns. We have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees, including allowing all employees to work remotely, suspending all non-essential travel worldwide for our employees, and discouraging employee attendance at industry events and in-person work-related meetings. These measures could negatively affect our business. For instance, temporarily requiring all employees to work remotely may disrupt our operations or increase the risk of a cybersecurity incident. Business disruptions, including those affecting our ongoing and planned clinical studies, may negatively affect the accuracy of our estimates regarding capital requirements and needs for additional financing or our ability to produce accurate and timely financial statements. We may incur additional liabilities related to business disruptions caused by COVID-19, including those related to our employees, our agreements with third parties, and our interactions with governmental authorities. COVID-19 has also caused volatility in the global financial markets and threatened a slowdown in the global economy, which may negatively affect our ability to raise additional capital on attractive terms or at all. In addition, a recession, depression, or other sustained adverse market event resulting from the spread of COVID-19 could materially and adversely affect our business and the value of our common stock.

The extent to which COVID-19 may impact our business will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration of the outbreak, the severity of COVID-19, or

the effectiveness of actions to contain and treat for COVID-19. We cannot presently predict the scope and severity of any potential business shutdowns or disruptions, including to our ongoing and planned clinical studies. Any such shutdowns or other business interruptions could result in material and negative effects to our ability to conduct our business in the manner and on the timelines presently planned, which could have a material adverse impact on our business, results of operation, and financial condition. To the extent the COVID-19 pandemic adversely affects our business, prospects, operating results, or financial condition, it may also have the effect of heightening many of the other risks described in this "Risk Factors" section.

We have incurred significant operating losses since our inception and anticipate we will incur continued losses for the foreseeable future.

We have funded our operations to date through proceeds from collaborations, grants, sales of convertible preferred stock and our initial public offering, or IPO, and follow-on offerings of our equity to the public. From our inception through December 31, 2020, we have received net proceeds of $357.0 million from such transactions. As of December 31, 2020, our cash and cash equivalents were $141.0 million. We have incurred net losses in each year since our inception, and we have an accumulated deficit of $213.0 million as of December 31, 2020. On January 20, 2021, the Company sold under the ATM offering an aggregate of 3,629,458 at a weighted-average price of $4.03 per share for net proceeds of $14.5 million after deducting sales commission and other offering expenses.

Substantially all of our operating losses have resulted from costs incurred in connection with general and administrative costs associated with our operations, and our research and development programs, including for our preclinical and clinical product candidates and our discovery platform. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses to significantly increase in connection with our clinical studies of our product candidates. In addition, if we obtain marketing approval for our product candidates, we will incur significant sales and marketing, legal, and outsourced-manufacturing expenses. In addition, we will incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of collaborations, strategic alliances, licensing arrangements, other marketing and distribution arrangements, equity offerings, royalty-based financing arrangements or debt financings. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt financing may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties or royalty-based financing arrangements, we may have to relinquish valuable rights to future revenue streams, research programs, or product candidates, or we may need to 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 commercialization or product development efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We have never generated any revenue from product sales, and we may never generate revenue or be profitable.

Our ability to become profitable depends upon the ability of our product candidates to generate revenue. To date, we have not generated any revenue from our product candidates, and we do not know when, or if, we will do so. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to sell, our current or future product candidates. Our ability to generate revenue depends on a number of factors, including, but not limited to:

- successfully completing preclinical and clinical development of our product candidates;
- identifying, assessing, and/or developing new product candidates from our NMDAr modulator discovery platform, or discovery platform;
- developing a sustainable and scalable manufacturing process for our product candidates, as well as establishing and maintaining commercially viable supply relationships with third parties that can provide adequate products and services to support clinical activities and commercial demand for our product candidates;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we successfully complete clinical development;
- launching and successfully commercializing product candidates for which we obtain regulatory and marketing approval, either by establishing a sales, marketing, and distribution infrastructure or collaborating with a partner;
- negotiating and maintaining an adequate price for our product candidates, both in the United States and in foreign countries where our products are commercialized;
- obtaining market acceptance of our product candidates as viable treatment options;
- building out new facilities or expanding existing facilities to support our ongoing development activity;
- addressing any competing technological and market developments;
- maintaining, protecting, expanding, and enforcing our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with drug development, we are unable to predict the timing or amount of our expenses, or when we will be able to generate any meaningful revenue or achieve or maintain profitability, if ever. In addition, our expenses could increase beyond our current expectations if we are required by the U.S. Food and Drug Administration, or FDA, or foreign regulatory agencies, to perform studies in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical studies or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, absent our entering into a collaboration or partnership agreement, we anticipate incurring significant costs associated with commercializing any approved product candidate and ongoing compliance efforts.

Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Revenue from the sale of any product candidate for which

regulatory approval is obtained will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, and whether we own the commercial rights for that territory. The precise number of people with painful diabetic peripheral neuropathy, or DPN, fibromyalgia, post-traumatic stress disorder, or PTSD, and Parkinson's disease mild cognitive impairment is unknown. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our drug candidates, are based on estimates. If the number of addressable patients is not as significant as we anticipate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice, or treatment guidelines, we may not generate significant revenue from sales of our product candidates, even if approved. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates, or continue our operations and cause a decline in the value of our common stock, all or any of which may adversely affect our viability.

Due to the significant resources required for the development of our discovery platform and pipeline, and depending on our ability to access capital, we must prioritize development of certain product candidates. Moreover, we may fail to expend our limited resources on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

We currently have three lead product candidates, NYX-2925, NYX-783, and NYX-458. We seek to maintain a process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing product candidates and ensuring replenishment of our portfolio.

Due to the significant resources required for the development of our product candidates, we must focus on specific diseases and disease pathways and decide which product candidates to pursue and advance and the amount of resources to allocate to each. Our decisions concerning the allocation of research, development, collaboration, management, and financial resources toward particular product candidates or therapeutic areas may not lead to the development of any viable commercial product and may divert resources away from better opportunities. If we make incorrect determinations regarding the viability or market potential of any of our product candidates or misread trends in the biopharmaceutical industry, in particular for disorders of the brain and nervous system, our business, financial condition, and results of operations could be materially adversely affected. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue, or relinquish valuable rights to such product candidates through collaboration, licensing, or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights.

Risks related to product development and commercialization

Research and development of biopharmaceutical products is inherently risky.

We are at an early stage of development of the product candidates currently in our pipeline and are continuing to discover additional potential product candidates leveraging our discovery platform. To date, we have devoted substantially all of our efforts and financial resources to identify, secure intellectual property for, and develop our discovery platform and our product candidates, including conducting multiple preclinical and clinical studies, and providing general and administrative support for these operations. Our business depends heavily on the successful preclinical and clinical development, regulatory approval, and commercialization of our product candidates. None of our product candidates have advanced into late-stage development or a pivotal clinical study and it may be years before any such study is initiated, if at all. NYX-2925, NYX-783, and NYX-458 will require substantial additional clinical development, testing, and regulatory approval before we are permitted to commence their commercialization. Further, we cannot be certain that any of our product candidates will be successful in clinical studies.

Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize our product candidates, and we may fail to do so for many reasons, including the following:

- our product candidates may not successfully complete preclinical or clinical studies, including as a result of disruptions related to COVID-19;
- a product candidate may, upon 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;
- our competitors may develop therapeutics that render our product candidates obsolete or less attractive;
- our competitors may develop platform technologies that render our platform technology obsolete or less attractive;
- the product candidates that we develop, and our discovery platform may not be sufficiently covered by intellectual property for which we hold exclusive rights;
- the market for a product candidate may change so that the continued development of that product candidate is no longer reasonable or commercially attractive;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- we may not be able to establish manufacturing capabilities or arrangements with third-party manufacturers for clinical and, if approved, commercial study;
- even if a product candidate obtains regulatory approval, we may be unable to establish sales and marketing capabilities, or successfully market such approved product candidate, to gain market acceptance; and
- a product candidate may not be accepted as safe or effective by patients, the medical community or third-party payors, if applicable.

If any of these events occur, we may be forced to abandon our development efforts for a product candidate or candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations. For instance, if we observe harmful side effects or other characteristics that indicate one product candidate is unlikely to be effective or otherwise does not meet applicable regulatory criteria, these findings may implicate the discovery platform as a whole.

We may not be successful in our efforts to further develop our discovery platform technology and current product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. Each of our product candidates is in the early stages of development and will require significant additional clinical development, management of preclinical, clinical, and manufacturing activities, regulatory approval, adequate manufacturing supply, a commercial organization, and significant marketing efforts before we generate any revenue from product sales, if at all.

The nonclinical and clinical studies for our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States, and in other countries where we intend to test and, if approved, market any product candidate. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must, among other requirements, demonstrate through preclinical studies and clinical studies that the product candidate is safe and effective for use in each target indication. Drug development is a long, expensive, and uncertain process, and delay or failure can occur at

any stage of any of our clinical studies. This process can take many years and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and preclinical studies and clinical studies, we cannot assure you that any of our product candidates will be successfully developed or commercialized.

If any of our product candidates successfully complete clinical studies, we generally plan to seek regulatory approval to market our product candidates in the United States, the European Union, or EU, and in additional foreign countries where we believe there is a viable commercial opportunity and significant patient need. We have never commenced, compiled, or submitted an application seeking regulatory approval to market any product candidate. We may never receive regulatory approval to market any product candidates even if such product candidates successfully complete clinical studies, which would adversely affect our viability. To obtain regulatory approval in countries outside the United States, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing and controls, clinical studies, commercial sales, pricing, and distribution of our product candidates. We may also rely on collaborators or partners to conduct the required activities to support an application for regulatory approval, and to seek approval, for one or more of our product candidates. We cannot be sure that any collaborators or partners will conduct these activities or do so within the timeframe we desire. Even if we (or any collaborators or partners) are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected.

Even if we receive regulatory approval to market any of our product candidates, we cannot assure you that any such product candidate will be successfully commercialized, widely accepted in the marketplace, or more effective than other commercially available alternatives.

Investment in biopharmaceutical product development involves significant risk that any product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval, and become commercially viable. We cannot provide any assurance that we will be able to successfully advance any of our product candidates through the development process or, if approved, successfully commercialize any of our product candidates.

We may not be successful in our efforts to continue to create a pipeline of product candidates or to develop commercially successful products. If we fail to successfully identify and develop additional product candidates, our commercial opportunity may be limited.

One of our strategies is to identify and pursue clinical development of additional product candidates. We currently have several compounds in the research, discovery, screening, and preclinical stages of development. Identifying, developing, obtaining regulatory approval, and commercializing additional product candidates for the treatment of disorders of the brain and nervous system will require substantial additional funding and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully identify or acquire additional product candidates, advance any of these additional product candidates through the development process, successfully commercialize any such additional product candidates, if approved, or assemble sufficient resources to identify, acquire, develop or, if approved, commercialize additional product candidates. If we are unable to successfully identify, acquire, develop, and commercialize additional product candidates, our commercial opportunity may be limited.

We may not be able to conduct, or contract others to conduct, animal testing in the future, which could harm our research and development activities.

Certain laws and regulations relating to drug development require us to test our product candidates on animals before initiating clinical studies involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted or delayed.

We have concentrated our research and development efforts on the treatment of disorders of the brain and nervous system, a field that has seen limited success in drug development. Further, our product candidates are based on new approaches and novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.

We have focused our research and development efforts on addressing disorders of the brain and nervous system, including painful DPN, fibromyalgia, PTSD, and Parkinson's disease cognitive impairment. Efforts by biopharmaceutical companies in the field of disorders of the brain and nervous system have seen limited successes in drug development. There are few effective therapeutic options available for patients with painful DPN, fibromyalgia, PTSD, or Parkinson's disease cognitive impairment. Our future success is highly dependent on the successful development of our discovery platform technology and our product candidates for treating disorders of the brain and nervous system. Developing and, if approved, commercializing our product candidates for treatment of disorders of the brain and nervous system subjects us to a number of challenges, including engineering product candidates and obtaining regulatory approval from the FDA and other regulatory authorities who have only a limited set of precedents to rely on.

Our approach to targeting the NMDAr is different from other antagonist and agonist agents currently being developed. Our proprietary compounds are designed to subtly modulate NMDArs. This strategy may not prove to be successful. We cannot be sure that our approach will yield satisfactory therapeutic products that are safe and effective, scalable, or profitable.

Moreover, public perception of drug safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical studies, or if approved, of physicians to prescribe our products.

We may encounter difficulties in enrolling subjects in our clinical studies, thereby delaying or preventing development of our product candidates.

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. We may experience difficulties in subject enrollment in our clinical studies for a variety of other reasons, including:

- disruptions related to COVID-19;
- the subject eligibility criteria defined in the protocol, including biomarker-driven identification and/or certain highly-specific criteria related to stage of disease progression, which may limit the patient populations eligible for our clinical studies to a greater extent than competing clinical studies for the same indication that do not have biomarker-driven patient eligibility criteria;
- eligibility requirements mandated by regulatory agencies which may limit the number of eligible patients in a given disorder;
- the size of the study population required for analysis of the study's primary endpoints;
- the proximity of subjects to a study site;
- the design of the study;
- our use of academic sites, which are less accustomed to running clinical studies and managing enrollment;
- public perception of drug safety issues;

- our ability to recruit clinical study investigators with the appropriate competencies and experience;
- competing clinical studies for similar therapies or targeting patient populations meeting our patient eligibility criteria;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies and product candidates;
- our ability to obtain and maintain patient consents; and
- the risk that subjects enrolled in clinical studies will not complete such studies, for any reason.

There is no precise method of establishing the actual number of people with disorders of the brain and nervous system in any geography over any time period. We estimate that neuropathic pain affects approximately 18 million people in the United States, and approximately 5.5 million of those suffer from painful DPN and more than 5 million suffer from fibromyalgia. It is estimated that over 8.5 million people suffer from PTSD. We estimate that more than half of the approximately 1 million people with Parkinson's disease in the United States suffer from either dementia or mild cognitive impairment. If the actual number of people with disorders of the brain and nervous system is lower than we believe, we may experience difficulty in enrolling subjects in our clinical studies, thereby delaying development of our product candidates.

We have experienced delays in subject enrollment as a result of a number of factors, including the COVID-19 pandemic and our enrollment criteria, in our painful DPN, fibromyalgia, PTSD, and Parkinson's disease studies. We may continue to experience enrollment delays as a result of these or other factors in our ongoing clinical studies. If we are unable to successfully enroll subjects in a timely way for the clinical studies for our product candidates, our clinical studies could be significantly delayed, which could materially affect our financial condition and results of operations.

Our clinical studies may fail to demonstrate adequate safety and efficacy of our product candidates, which would prevent, delay, or limit the scope of regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must, among other requirements, demonstrate through lengthy, complex, and expensive preclinical studies and clinical studies that our product candidates are both safe and effective for use in each target indication. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use.

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 study process, including as a result of external factors such as COVID-19. The results of preclinical studies of our product candidates may not be predictive of the results of early-stage or later-stage clinical studies, and results of early-stage clinical studies of our product candidates may not be predictive of the results of later-stage clinical studies. The results of clinical studies in one set of subject or disease indications may not be predictive of those obtained in another. In some instances, there can be significant variability in safety or efficacy results between different clinical studies of the same product candidate due to numerous factors, including changes in study procedures set forth in protocols, differences in the size and type of the patient populations, changes in and lack of adherence to the dosing regimen and other clinical study protocols, and the rate of dropout among clinical study participants. Product candidates in later stages of clinical studies may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical studies. A number of companies in the biopharmaceutical industry have suffered significant setbacks in later-stage clinical studies due to lack of efficacy or safety issues, notwithstanding promising results in early-stage studies. This is particularly true in disorders of the brain and nervous system, where failure rates historically have been higher than in other disease areas. Most product candidates that begin clinical studies are never approved by regulatory authorities for commercialization.

We may be unable to design and execute a clinical study to support marketing approval. We cannot be certain that our current clinical studies or any other future clinical studies will be successful. Additionally, any safety concerns observed

in any one of our clinical studies in our targeted indications could limit the prospects for regulatory approval of our product candidates in those, and other indications, which could have a material adverse effect on our business, financial condition, and results of operations.

In addition, even if such clinical studies are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more studies could be required before we submit our product candidates for approval. To the extent that the results of the studies are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional studies in support of potential approval of our product candidates. Even if regulatory approval is secured for any of our product candidates, the terms of such approval may limit the scope and use of our product candidates, which may also limit their commercial potential.

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

Serious adverse events or other undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies, and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other regulatory authorities.

Further, clinical studies by their nature utilize a sample of the potential patient population for a limited duration of exposure. Rare and severe side effects of a product candidate may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar products) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may suspend, withdraw, or limit their approval of such products;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;
- we may be required to change the way such products are distributed or administered;
- we may be required to conduct additional post-marketing studies and surveillance;
- we may be required to implement a risk evaluation and mitigation strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be subject to regulatory investigations and government enforcement actions;
- subjects in a clinical study may experience severe or unexpected drug related side effects;
- we may decide, or regulatory authorities may require us, to conduct additional clinical studies or abandon product development programs;
- we may decide to remove such products from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our products;
- the product may become less competitive; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates, could substantially increase the costs of commercializing our product candidates, and could significantly impact our ability to successfully commercialize our product candidates and generate revenues.

Failures or delays in the commencement or completion of, or ambiguous or negative results from, our ongoing or planned clinical studies of our product candidates could result in increased costs to us and could delay, prevent, or limit our ability to generate revenue and continue our business.

We do not know whether any of our ongoing or planned clinical studies will begin or be completed on schedule, if at all, as the commencement and completion of clinical studies can be delayed or prevented for a number of reasons, including, among others:

- disruptions related to COVID-19;
- the FDA or other regulatory bodies may not authorize us or our investigators to commence our planned clinical studies or any other clinical studies we may initiate, or may suspend our clinical studies, for example, through imposition of a clinical hold;
- delays in filing or receiving clearance of additional investigational new drug, or IND, applications that may be required;
- lack of adequate funding to continue our clinical studies and preclinical studies;
- negative results from our ongoing preclinical studies;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and study sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical studies, for example delays in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining ethics committee or Institutional Review Board, or IRB, approval to conduct a clinical study at a prospective site or sites;
- challenges in recruiting and enrolling subjects to participate in clinical studies, the proximity of subjects to study sites, eligibility criteria for the clinical study, including for example our strict enrollment criteria in certain of our studies, the nature of the clinical study protocol, the availability of approved effective treatments for the relevant disease, and competition from other clinical study programs for similar indications;
- severe or unexpected drug related side effects experienced by subjects in a clinical study;
- we may decide, or regulatory authorities may require us, to conduct additional clinical studies or abandon product development programs;
- delays in validating, or inability to validate, any endpoints utilized in a clinical study;
- the FDA may disagree with our clinical study design and our interpretation of data from clinical studies, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical studies;

- reports from preclinical or clinical testing of other NMDAr-dependent therapies that raise safety or efficacy concerns; and

- difficulties retaining subjects who have enrolled in a clinical study but may be prone to withdraw due to rigors of the clinical studies, lack of efficacy, side effects, personal issues, or loss of interest.

Clinical studies may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical study may be suspended or terminated by us, the FDA, the IRBs at the sites where the IRBs are overseeing a clinical study, a data and safety monitoring board, or DSMB, overseeing the clinical study at issue or other regulatory authorities due to a number of factors, including, among others:

- concerns related to COVID-19;

- failure to conduct the clinical study in accordance with regulatory requirements or our clinical protocols;

- inspection of the clinical study operations or study sites by the FDA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including in response to the imposition of a clinical hold;

- unforeseen safety issues, including any that could be identified in our ongoing preclinical or clinical studies, adverse side effects or lack of effectiveness;

- changes in government regulations or administrative actions;

- problems with clinical supply materials; and

- lack of adequate funding to continue clinical studies.

Changes in regulatory requirements, FDA guidance, or unanticipated events during our nonclinical studies and clinical studies of our product candidates may occur, which may result in changes to nonclinical or clinical study protocols or additional nonclinical or clinical study requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance, or unanticipated events during our nonclinical studies and clinical studies may force us to amend nonclinical studies and clinical study protocols or the FDA may impose additional nonclinical studies and clinical study requirements. Amendments or changes to our clinical study protocols would require resubmission to the FDA and IRBs for review and approval, which may adversely impact the cost, timing, or successful completion of clinical studies. Similarly, amendments to our nonclinical studies may adversely impact the cost, timing, or successful completion of those nonclinical studies. If we experience delays completing, or if we terminate, any of our nonclinical studies or clinical studies, or if we are required to conduct additional nonclinical or clinical studies, the commercial prospects for our product candidates may be harmed and our ability to generate product revenue will be delayed.

If, in the future, we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market any product candidates we may develop, we may not be successful in commercializing those product candidates if and when they are approved.

We do not currently have an infrastructure for the sales, marketing, and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial, and other non-technical capabilities, or make arrangements with third parties to perform these services. There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force or reimbursement

specialists is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and other commercialization capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our commercialization personnel.

If we enter into arrangements with third parties to perform sales, marketing, commercial support, and distribution services, our product revenue or the profitability of product revenue may be lower than if we were to market and sell any products we may develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to commercialize our product candidates or may be unable to do so on terms that are favorable to us. We may have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish commercialization capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates if approved.

If we are unable to establish adequate sales, marketing, and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition, and prospects will be materially adversely affected.

Even if we receive marketing approval for our product candidates, our product candidates may not achieve broad market acceptance by physicians, patients, healthcare payors, or others in the medical community, which would limit the revenue that we generate from their sales.

The commercial success of our product candidates, if approved by the FDA or other applicable regulatory authorities, will depend upon the awareness and acceptance of our product candidates among the medical community, including physicians, patients, and healthcare payors. If any of our product candidates are approved but do not achieve an adequate level of acceptance by physicians, patients, healthcare payors, and others in the medical community, we may not generate sufficient revenue to become or remain profitable. Market acceptance of our product candidates, if approved, will depend on a number of factors, including, among others:

- the safety, efficacy, and other potential advantages of our approved product candidates compared to other available therapies;
- limitations or warnings contained in the labeling approved for our product candidates by the FDA or other applicable regulatory authorities;
- any restrictions on the use of our products together with other medications;
- the prevalence and severity of any adverse effects associated with our product candidates;
- inability of certain types of patients to take our products;
- the clinical indications for which our product candidates are approved;
- availability of alternative treatments already approved or expected to be commercially launched in the near future;
- the potential and perceived advantages of our approved product candidates over current treatment options or alternative treatments, including future alternative treatments;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of our product candidates through sales and marketing efforts;
- our ability to obtain sufficient third-party payor coverage or reimbursement; or
- the willingness of patients to pay out-of-pocket in the absence of third-party payor coverage.

If our product candidates are approved but do not achieve an adequate level of acceptance by patients, physicians, and payors, we may not generate sufficient revenue from our product candidates to become or remain profitable. Before granting reimbursement approval, healthcare payors may require us to demonstrate that our product candidates, in addition to treating these target indications, also provide incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of our product candidates may require significant resources and may never be successful.

Even if we obtain regulatory approval for our product candidates, our products will remain subject to extensive regulatory scrutiny.

Even if we receive marketing approval for our product candidates, regulatory authorities may still impose significant restrictions on our product candidates, indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies. If any of our product candidates are approved, they will be subject to ongoing regulatory requirements, including for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-marketing information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive requirements imposed by the FDA and comparable foreign regulatory authorities, including, for example, ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practice, or cGMP, regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any new drug application, or NDA, or comparable marketing approval. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

The FDA has significant post-marketing authority, including, for example, the authority to require labeling changes based on new safety information and to require post-marketing studies or clinical studies to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post-approval, the submission of a REMS. Many chronic pain therapies have been recognized as drugs of abuse and require REMS. For example, while NYX-2925 has been well tolerated in clinical studies to date and has shown low abuse potential in preclinical drug discrimination and abuse liability studies, the FDA may still determine that NYX-2925 requires a REMS program. Any REMS required by the FDA may lead to increased costs to assure compliance with new post-approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue.

Any regulatory approvals that we receive for our product candidates will be subject to limitations on the approved indicated uses for which the product may be marketed and promoted or to the conditions of approval (including the

requirement to implement a REMS), or contain requirements for potentially costly post-marketing testing. We will be required to report certain adverse reactions and production problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. The FDA and other agencies, including the U.S. 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. We will have to comply with requirements concerning advertising and promotion for our products. 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 label. As such, we may not promote our products for indications or uses for which they do not have approval. The holder of an approved NDA or comparable marketing approval must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. We could also be asked to conduct post-marketing studies or clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, such regulatory agency may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may, among other things:

- issue warning or untitled letters that would result in adverse publicity;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approvals;
- suspend any of our ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products; or
- request that we initiate a product recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

We face significant competition in an environment of rapid technological and scientific change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer, more advanced, or more effective than ours, which may negatively impact our ability to successfully market or commercialize any product candidates we may develop and ultimately harm our financial condition.

The development and commercialization of new drug products is highly competitive. Moreover, treating brain and nervous system disorders is characterized by strong and increasing competition, with a strong emphasis on intellectual property. We may face competition with respect to any product candidates that we seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. 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.

Companies that we are aware are developing or commercializing NMDAr-targeted therapies include companies with significant financial and/or scientific resources, such as Acadia Pharmaceuticals Inc., Adamas Pharmaceuticals Inc., Allergan plc (now a subsidiary of AbbVie Inc.), Avanir Pharmaceuticals, Inc., Axsome Therapeutics, Inc., Biohaven Pharmaceutical Holding Co. Ltd., Cadent Therapeutics, Inc., Cerecor Inc., Eli Lilly and Company, Genentech Inc., Intra-Cellular Therapies, Inc., Janssen Pharmaceuticals, Inc., NeuroRx, Inc., Newron Pharmaceuticals S.p.A., Otonomy, Inc., Relmada Therapeutics, Inc., Sage Therapeutics, Inc., UCB S.A., Gate Neurosciences, Inc., and Vistagen Therapeutics, Inc.

Many of our current or potential competitors, either alone or with their strategic partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical studies, obtaining regulatory approvals, and marketing approved products than we do. 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 or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Furthermore, currently approved products could be discovered to have application for treatment of disorders of the brain and nervous system indications, which could give such products significant regulatory and market timing advantages over any of our product candidates. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours and may obtain orphan product exclusivity from the FDA for indications our product candidates are targeting, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, products or technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

In addition, we could face litigation or other proceedings with respect to the scope, ownership, validity and/or enforceability of our patents relating to our competitors' products and our competitors may allege that our products infringe, misappropriate, or otherwise violate their intellectual property. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. See "Risks related to our intellectual property rights."

Even if we receive marketing approval for our product candidates in the United States, we may never receive regulatory approval to market our product candidates outside of the United States.

In order to market any product outside of the United States, we must establish and comply with the numerous and varying safety, efficacy, and other regulatory requirements of other countries. Approval procedures vary among countries and can involve additional product candidate testing and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in substantial delays in bringing products to market in such countries. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process in others. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market our product candidates in such foreign markets. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, results of operations, and prospects.

Risks related to regulatory approval and other legal compliance matters

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

The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, typically takes many years following the commencement of clinical studies, and depends upon numerous factors, including the type, complexity, and novelty of the product candidates involved. As of June 23, 2020, the FDA noted it is continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals; however, FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions FDA is unable to complete such required inspections during the review period. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications.

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, which may cause delays in the approval or the decision not to approve an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. Moreover, the FDA or other regulatory authorities may fail to approve companion diagnostics that we contemplate using with our therapeutic product candidates. We have not submitted for, or obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

Applications for our product candidates could fail to receive regulatory approval for many reasons, including but not limited to the following:

- the FDA or comparable foreign regulatory authorities may raise concerns with the quality, completeness, and interpretability of our clinical data as a result of COVID-19-related disruptions in clinical studies;
- the FDA or comparable foreign regulatory authorities may disagree with the design, implementation, or results of our clinical studies;
- the FDA or comparable foreign regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective, or have undesirable or unintended side effects, toxicities, or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical studies;
- the data collected from clinical studies of our product candidates may not be sufficient to support the submission of an NDA or other submission, or to obtain regulatory approval in the United States or elsewhere;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;

- the FDA or comparable foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes, test procedures and specifications, 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 the results of clinical studies, may result in our failing to obtain regulatory approval to market any of our product candidates, which would significantly harm our business, results of operations, and prospects.

We are subject to healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits and future earnings.

Although we do not currently have any products on the market, once we begin commercializing our products, we may be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. Healthcare providers, physicians, and others will play a primary role in the recommendation and prescription of our product candidates, if approved. Our future arrangements with third-party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell, and distribute our product candidates, if we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti Kickback Statute, or AKS, prohibits, among other things, persons from knowingly and willfully soliciting, offering, 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, arrangement or recommendation of, any good or service, for which payment may be made under federal healthcare programs 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 AKS 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 AKS constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or federal civil money penalties statute. On December 2, 2020, the Office of Inspector General, or OIG, published further modifications to the AKS. Under the final rules, OIG added safe harbor protections under the AKS for certain coordinated care and value-based arrangements among clinicians, providers, and others. This rule (with exceptions) became effective January 19, 2021. Implementation of this change and new safe harbors for point-of-sale reductions in price for prescription pharmaceutical products and pharmacy benefit manager service fees are currently under review by the Biden administration and may be amended or repealed. We continue to evaluate what effect, if any, the rule will have on our business;

- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for 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 AKS, 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 and Clinical Health Act, or HITECH, and its implementing regulations, imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," those independent contractors or agents of covered entities that create, receive, maintain, transmit or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

- the federal transparency requirements, sometimes referred to as the "Sunshine Act," under the Patient Protection and Affordable Care Act, or the ACA, require manufacturers of drugs, devices, biologics, and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report to the Department of Health and Human Services, or HHS, information related to physician (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) payments and other transfers of value and teaching hospitals, as well as physician ownership and investment interests, including such interests held by their immediate family. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, 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 drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing. Data privacy and security laws and regulations in foreign jurisdictions may be more stringent than those in the United States (such as the European Union, which adopted the General Data Protection Regulation, which became effective in May 2018). State laws may govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales team, were 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, and exclusion from government funded healthcare programs, such as Medicare and Medicaid, individual imprisonment, reputational harm, and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs.

Data collection in Europe and some U.S. states are governed by restrictive regulations governing the use, processing, and cross-border transfer of personal information.

The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers. The GDPR increased our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities. Further, the United Kingdom's decision to leave the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated now that the United Kingdom has left the EU.

If any of our product candidates obtain regulatory approval, additional competitors could enter the market with generic versions of such drugs, which may result in a material decline in sales of affected products.

Under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved, small-molecule innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit an NDA, under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act that references the FDA's prior approval of the small-molecule innovator product. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. The Hatch-Waxman Act also provides for certain periods of regulatory exclusivity, which preclude FDA approval (or in some circumstances, FDA filing and reviewing) of an ANDA or 505(b)(2) NDA. These include, subject to certain exceptions, the period during which an FDA-approved drug is subject to orphan drug exclusivity. For example, a drug that is granted regulatory approval may be eligible for five years of marketing exclusivity in the United States following regulatory approval if that drug is classified as a new chemical entity, or NCE. A drug can be classified as a NCE if the FDA has not previously approved any other drug containing the same active moiety. While we believe there is a likelihood that the FDA would grant NCE status to both NYX-2925 and NYX-783 if both are granted regulatory approval, NYX-2925 and NYX-783 have the same structural formula but differ in spatial orientation, i.e., are separate stereoisomers of each other, and there can be no assurance that both will be granted NCE exclusivity.

In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the "Orange Book." If there are patents listed in the Orange Book, a generic or 505(b)(2) applicant that seeks to market its product before expiration of the patents must include in the ANDA a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Appropriate notice of the certification must be given to the innovator, too, and if within 45 days of receiving such notice the innovator sues to protect its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, if any of our product candidates are approved, competitors could file ANDAs for generic versions of our small-molecule drug products or 505(b)(2) NDAs that reference our small-molecule drug products, respectively. If there are patents listed for our small-molecule drug products in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any of our owned patents that are listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could immediately face generic competition and its sales would likely decline rapidly and materially. See "Risks related to our intellectual property rights."

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If we are found to have improperly promoted off-label uses, we may become subject to significant liability.

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as NYX-2925, NYX-783, and NYX-458, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. For example, if we receive marketing approval for NYX-2925 as a treatment for painful DPN, physicians may nevertheless prescribe NYX-2925 to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Even if approved, reimbursement policies could limit our ability to sell our product candidates.

In the United States and markets in other countries, patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Market acceptance and sales of our product candidates will depend on reimbursement policies and may be affected by healthcare reform measures. Our ability to successfully commercialize our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. 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 for those medications. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If coverage and adequate 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 a sufficient return on our investment.

There is also significant uncertainty related to the insurance coverage and reimbursement of newly approved products and coverage may be more limited than the purposes for which the medicine is approved by the FDA or comparable foreign regulatory authorities. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree.

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.

Cost containment is a primary concern in the U.S. healthcare industry and elsewhere. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that reimbursement will be available for our product candidates and, if reimbursement is available, the level of such reimbursement. Reimbursement may impact the demand for, or the price of, our product candidates. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates.

In some foreign countries, particularly in Canada and European countries, the pricing of prescription pharmaceuticals is subject to strict governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical study that compares the cost-effectiveness of our product candidates with other available therapies. If reimbursement for our product candidates is unavailable in any country in which we seek reimbursement, if it is limited in scope or amount, if it is conditioned upon our completion of additional clinical studies, or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars; 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; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjected manufacturers to new annual fees and taxes for certain branded prescription drugs; created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and provided incentives to programs that increase the federal government's comparative effectiveness research.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing legal and constitutional challenges in the United States Supreme Court. Additionally, the former Trump Administration issued various Executive Orders which eliminated cost sharing subsidies and Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business, especially given the new administration.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, and, due to subsequent legislative amendments, will remain in effect

through 2030 unless additional Congressional action is taken. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, also known as the CARES Act, as well as subsequent legislation, these reductions have been suspended from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic. Proposed legislation, if passed, would extend this suspension until the end of the pandemic.

The former Trump administration's budget proposal for fiscal year 2021 included a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the former Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the former Trump administration also previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions after January 20, 2021.

In 2020, former President Trump announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. The FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021, and ending December 31, 2027. However, in response to a lawsuit filed by several industry groups, on December 28, the U.S. District Court for the Northern District of California issued a nationwide preliminary injunction enjoining government defendants from implementing the MFN Rule pending completion of notice-and-comment procedures under the Administrative Procedure Act. On January 13, 2021, in a separate lawsuit brought by industry groups in the U.S. District of Maryland, the government defendants entered a joint motion to stay litigation on the condition that the government would not appeal the preliminary injunction granted in the U.S. District Court for the Northern District of California and that performance for any final regulation stemming from the MFN Interim Final Rule shall not commence earlier than 60 days after publication of that regulation in the Federal Register. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the MFN Model may materially and adversely affect the price we receive for any of our product candidates. Additionally, on December 2, 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 an order entered by the U.S. District Court for the District of Columbia, the portion of the rule eliminating safe harbor protection for certain rebates related to the sale or purchase of a pharmaceutical product from a manufacturer to a plan sponsor under Medicare Part D has been delayed to January 1, 2023. Further, implementation of this change and new safe harbors for point-of-sale reductions in price for prescription pharmaceutical products and pharmacy benefit manager service fees are currently under review by the Biden administration and may be amended or repealed.

Further, 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.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Existing and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some 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 marketing approval.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality, and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. We expect that these and any healthcare reform measures that may be adopted in the future may result in reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies, and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Additionally, we may face competition in the United States from therapies sourced from foreign countries that have placed price controls on pharmaceutical products. Legislation or regulations allowing the reimportation of drugs into the United States, if enacted, could decrease the price we receive for any products that we may develop and adversely affect our future revenues and prospects for profitability.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for approved products. In addition, there have been several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare and reform government program reimbursement methodologies for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent labeling and post-marketing testing and other requirements.

It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing health care legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations, and other health care payors to contain or reduce costs of health care may adversely affect the demand for any product candidates for which we may obtain regulatory approval, our ability to set a price that we believe is fair for our products, our ability to obtain coverage and reimbursement approval for a product, our ability to generate revenue and achieve or maintain profitability, and the level of taxes that we are required to pay.

Our future growth may depend, in part, on our ability to commercialize our product candidates in foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability may depend, in part, on our ability to commercialize our product candidates in foreign markets for which we may rely on collaboration with third parties. If we commercialize our product candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for our product candidates in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting, and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- the existence of additional potentially relevant third-party intellectual property rights;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of our product candidates could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions, and changes in tariffs.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

In order to market any product outside of the United States, however, we must establish and comply with the numerous and varying safety, efficacy, and other regulatory requirements of other countries. Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA or other comparable foreign regulatory authority grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing, and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical studies as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States, as well as other risks. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties, and costs for us and could delay or prevent the introduction of our products in certain countries. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market our product candidates in such foreign markets. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, results of operations, and prospects.

Our employees, independent contractors, consultants, commercial partners, and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud, misconduct, or other illegal activity by our employees, independent contractors, consultants, commercial partners, and vendors. Misconduct by these parties could include intentional, reckless, and negligent conduct that fails to: comply with the laws of the FDA and other comparable foreign regulatory authorities; provide true, complete and accurate information to the FDA and other comparable foreign regulatory authorities; comply with manufacturing standards we have established; comply with healthcare fraud and abuse laws in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. In particular, sales, marketing, and other business arrangements in the healthcare industry are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing, and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales and commission, certain customer incentive programs, and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter misconduct by employees and third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws. 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, including the imposition of significant fines or other sanctions.

If we or any contract manufacturers and suppliers we engage fail to comply with environmental, health, and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We and any contract manufacturers and suppliers we engage are subject to numerous federal, state, and local environmental, health, and safety laws, regulations, and permitting requirements, including those governing laboratory procedures; the generation, handling, use, storage, treatment, and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air, and water; and employee health and safety. Under certain environmental laws, we could be held responsible for costs relating to any contamination at our current or past facilities and at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

We could be adversely affected by violations of the U.S. Foreign Corrupt Practices Act, or FCPA, and other worldwide anti-bribery laws.

We are subject to the FCPA, which prohibits companies and their intermediaries from making payments in violation of law to non-U.S. government officials for the purpose of obtaining or retaining business or securing any other improper advantage. We have an ongoing relationship with Sai Life Sciences Ltd., or Sai, a non-U.S. company, as a third-party supplier of custom chemical synthesis of the compounds used in our product candidates such as spiro-beta lactam. Our significant reliance on a foreign supplier demands a high degree of vigilance in preventing our employees and consultants from participation in corrupt activity, because this supplier could be deemed our agent, and we could be held responsible for its actions. The FCPA and similar anti-bribery laws to which we may be subject are complex and far-reaching in nature, and, as a result, we cannot assure you that we would not be required in the future to alter one or

more of our practices to be in compliance with these laws or any changes in these laws or the interpretation thereof. Any violations of these laws, or allegations of such violations, could disrupt our operations, involve significant management distraction, and involve significant costs and expenses, including legal fees. We could also suffer severe penalties, including criminal and civil penalties, disgorgement, and other remedial measures.

Risks related to collaborations with third parties

We may depend on collaborations with third parties for the research, development, and commercialization of certain product candidates we may develop. If any such collaborations are not successful, we may not be able to realize the market potential of those product candidates.

We may seek third-party collaborators for the research, development, and commercialization of certain product candidates we plan to develop. Our likely collaborators for any other collaboration arrangements include large and mid-size pharmaceutical companies, biotechnology companies, or academic institutions. If we enter into any such arrangements with any third parties, we will likely have shared or limited control over the amount and timing of resources that our collaborators dedicate to the development or potential commercialization of any product candidates we may seek to develop with them. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any collaboration that we enter into.

Collaborations involving our research programs, or any product candidates we may develop, pose the following risks to us:

- collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not properly obtain, maintain, enforce, or defend intellectual property or proprietary rights relating to our product candidates or research programs or may use our proprietary information in such a way as to expose us to potential litigation or other intellectual property related proceedings, including proceedings challenging the scope, ownership, validity, and enforceability of our intellectual property;
- collaborators may own or co-own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right or any right to commercialize such intellectual property or such product candidates or research programs;
- we may need the cooperation of our collaborators to enforce or defend any intellectual property we contribute to or that arises out of our collaborations, which may not be provided to us;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of our product candidates or research programs or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborators may decide not to pursue development and commercialization of any product candidates we develop or may elect not to continue or renew development or commercialization programs based on clinical study results, changes in the collaborator's strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical studies, provide insufficient funding for a clinical study program, stop a clinical study or abandon a product candidate, repeat or conduct new clinical studies, 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 or research programs if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidates;
- we may lose certain valuable rights under circumstances identified in our collaborations, including if we undergo a change of control;
- collaborators may undergo a change of control and the new owners may decide to take the collaboration in a direction which is not in our best interest;
- collaborators may become bankrupt, which may significantly delay our research or development programs, or may cause us to lose access to valuable technology, know-how, or intellectual property of the collaborator relating to our products, product candidates, or research programs;
- key personnel at our collaborators may leave, which could negatively impact our ability to productively work with our collaborators;
- collaborations may require us to incur short and long-term expenditures, issue securities that dilute our stockholders, or disrupt our management and business;
- 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 or our discovery platform; and
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our development or commercialization program under such collaboration could be delayed, diminished, or terminated.

In addition, the terms and conditions of collaboration agreements may involve complex legal, business and scientific issues, and certain provisions may be susceptible to multiple interpretations. As with any complex contractual arrangement, disputes may arise between us and our collaborators regarding the terms and conditions of these agreements, including with respect to the scope of rights granted to, or restrictions placed on, each party under these agreements. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights under the agreement, or increase what we believe to be our obligations under the relevant agreement, either of which could materially harm our business, financial condition, results of operations, and prospects.

Moreover, we may face significant competition in seeking appropriate collaborations. Recent business combinations among biotechnology and pharmaceutical companies have resulted in a reduced number of potential collaborators. In addition, the negotiation process is time-consuming and complex, and we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we 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 product candidates or bring them to market and generate product revenue.

If we enter into collaborations to develop and potentially commercialize any product candidates, we may not be able to realize the benefit of such transactions if we or our collaborator elects not to exercise the rights granted under the agreement or if we or our collaborator are unable to successfully integrate a product candidate into existing operations and company culture. In addition, if our agreement with any of our collaborators terminates, our access to technology and intellectual property licensed to us by that collaborator may be restricted or terminate entirely, which may delay our continued development of our product candidates utilizing the collaborator's technology or intellectual property or require us to stop development of those product candidates completely. We may also find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. Many of the risks relating to product development, regulatory approval, and commercialization described in this "Risk factors" section also apply to the activities of our collaborators and any negative impact on our collaborators may adversely affect us.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

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 design or results of clinical studies, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of any collaborations or other arrangements that we may establish may not be favorable to us.

In addition, any future collaborations that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

Exclusivity and other governance provisions within our agreements with Allergan may prevent us from pursuing alternative product candidates and exercising complete control over our product candidates' development.

Pursuant to the research collaboration agreement, or Allergan Research Collaboration Agreement, we entered into with Allergan plc, or Allergan, pursuant to which we and Allergan received research, development, and commercial rights to compounds discovered using our discovery platform, during the license period for the relevant compounds are set forth in the Allergan Research Collaboration Agreement we may not alone, or with a third party, directly or indirectly engage in (a) the research or preclinical development of any compound or any product for the purpose of the treatment, prevention or diagnosis of any disorders or conditions in a specified field, which is defined as any therapeutic, prophylactic, or diagnostic use for certain delineated psychiatric or neurocognitive disorders or conditions, and which we refer to as Allergan's Field, (b) the clinical development of any compound or any product for the treatment, prevention or diagnosis of any disorders and conditions in Allergan's Field, or the manufacture of such compound or product for such purpose, or (c) the commercialization of any compound or any product labelled, or approved or licensed by any regulatory authority, for the treatment, prevention, or diagnosis of any disorders or conditions in Allergan's Field, or the manufacture of such compound or product. By their terms, these field-related restrictions pertaining to Allergan's license rights survive the expiration of the Allergan Research Collaboration Agreement and the exclusivity period set forth in

the agreement. We are bound by a similar set of restrictions on our research, development, and commercialization activities with respect to compounds and products in Allergan's Field under an asset contribution agreement that we entered into with Allergan in connection with Allergan's acquisition of Naurex. Except with respect to compounds for which Allergan exercises its option under the Allergan Research Collaboration Agreement, Allergan is not precluded under the Allergan Research Collaboration Agreement or the asset contribution agreement from competing with us outside of Allergan's Field. These exclusivity provisions may inhibit our development efforts and may materially harm our business, financial condition, results of operations, and prospects.

Risks related to our reliance on third parties

We rely, and expect that we will continue to rely, on third parties to conduct any clinical studies for our product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We do not have the ability to independently conduct clinical studies. We rely on medical institutions, clinical investigators, contract laboratories, and other third parties, such as CROs, to conduct clinical studies on our product candidates. For example, we are party to a sponsored research agreement with Northwestern University, or Northwestern, through which Northwestern has historically furnished the laboratory facilities and equipment necessary to conduct certain research projects and related clinical studies. We may need to enter into future agreements with Northwestern or other third parties, under which we would have less control over the maintenance of the facility. We enter into agreements with third-party CROs to provide monitors for and to manage data for our ongoing clinical studies. We rely heavily on these parties for execution of clinical studies for our product candidates and control only certain aspects of their activities. As a result, we have less direct control over the conduct, timing, and completion of these clinical studies and the management of data developed through clinical studies than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- experience business disruptions as a result of COVID-19;
- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical studies and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific requirements and standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with regulations and guidelines, including Good Clinical Practices, or GCPs, for conducting, monitoring, recording, and reporting the results of clinical studies to ensure that the data and results are scientifically credible and accurate, and that the study patients are adequately informed of the potential risks of participating in clinical studies. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical study sponsors, principal investigators and study sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical studies may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical studies before approving our marketing applications. We cannot assure you that, upon

inspection, the FDA will determine that any of our clinical studies comply with GCPs. In addition, our clinical studies must be conducted with product candidates produced under cGMP regulations and will require a large number of test patients. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical studies, which would delay the regulatory approval process and could also subject us to enforcement action up to and including civil and criminal penalties.

Although we do design our clinical studies for our product candidates, CROs conduct all of the clinical studies. As a result, many important aspects of our drug development programs are outside of our direct control. In addition, the CROs may not perform all of their obligations under arrangements with us or in compliance with regulatory requirements, but we remain responsible and are subject to enforcement action that may include civil penalties and criminal prosecution for any violations of FDA laws and regulations during the conduct of our clinical studies. If the CROs do not perform clinical studies in a satisfactory manner, breach their obligations to us, or fail to comply with regulatory requirements, the development and commercialization of our product candidates may be delayed or our development program materially and irreversibly harmed. We cannot control the amount and timing of resources these CROs devote to our program or our clinical products. If we are unable to rely on clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of our clinical studies and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If our collaboration is delayed or terminated or our ability to continue to use the current research space is terminated as a result of conflicts of interest, we may not be able to continue our planned research projects and related clinical studies on the expected timeline and may need to spend significant time and efforts to secure alternative lab facilities and equipment. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical studies such CROs are associated with may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, we believe that our financial results and the commercial prospects for our product candidates in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

The manufacture of our product candidates, particularly those that utilize our discovery platform, is complex and we may encounter difficulties in production. If we or any of our third-party manufacturers encounter such difficulties, or fail to meet rigorously enforced regulatory standards, our ability to provide supply of our product candidates for clinical studies or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

The processes involved in manufacturing our drug product candidates, particularly those that utilize our discovery platform, are complex, expensive, highly-regulated, and subject to multiple risks. Further, as product candidates are developed through preclinical studies to late-stage clinical studies towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical studies or other future clinical studies.

In addition, the manufacturing process for any products that we may develop is subject to FDA and other comparable foreign regulatory authority approval processes and continuous oversight, and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements, including, for example, complying with cGMPs, on an ongoing basis. If we or our third-party manufacturers are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our contract manufacturers will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical studies, require bridging clinical studies or the repetition of one or more

clinical studies, increase clinical study costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations, and growth prospects.

We rely completely on third-party suppliers to manufacture our clinical drug supplies for our product candidates, and we intend to rely on third parties to produce preclinical, clinical, and commercial supplies of any future product candidates.

We do not currently have, nor do we plan to acquire, the infrastructure or capability to internally manufacture our clinical drug supply of our product candidates, or any future product candidates, for use in the conduct of our preclinical studies and clinical studies, and we lack the internal resources and the capability to manufacture any product candidates on a clinical or commercial scale. The facilities used by our contract manufacturers to manufacture the active pharmaceutical ingredient and final drug product must complete a pre-approval inspection by the FDA and other comparable foreign regulatory agencies to assess compliance with applicable requirements, including cGMPs, after we submit our NDA or relevant foreign regulatory submission to the applicable regulatory agency.

We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers to comply with cGMPs for manufacture of both active drug substances and finished drug products. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or applicable foreign regulatory agencies, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over our contract manufacturers' ability to maintain adequate quality control, quality assurance, and qualified personnel. Furthermore, all of our contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such materials and products. For example, our product candidates are spiro-beta lactams which may require our manufacturers to manufacture them in specifically isolated facilities. If our contract manufacturers cannot successfully manufacture material, such as spiro-beta lactams, that conforms to our specifications and the strict regulatory requirements of the FDA or applicable foreign regulatory agencies, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. As a result, failure to satisfy the regulatory requirements for the production of those materials and products may affect the regulatory clearance of our contract manufacturers' facilities generally. If the FDA or an applicable foreign regulatory agency determines now or in the future that these facilities for the manufacture of our product candidates are noncompliant, we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market our product candidates. Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information. We are also unable to predict how changing global economic conditions or potential global health concerns such as COVID-19 will affect our third-party suppliers and manufacturers. Any negative impact of such matters on our third-party suppliers and manufacturers may also have an adverse impact on our results of operations or financial condition.

We do not have long-term supply agreements in place with our contractors, and each batch of our product candidates is individually contracted under a quality and supply agreement. If we engage new contractors, such contractors must complete an inspection by the FDA and other applicable foreign regulatory agencies. We plan to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of our product candidates, if approved. Our current scale of manufacturing is adequate to support all of our needs for preclinical studies and clinical study supplies.

We are dependent on single-source suppliers for some of the components and materials used in, and the processes required to develop, our product candidates.

We currently depend on single-source suppliers for our active ingredients used in, and processes required to develop, our product candidates. In particular, we rely on Sai to produce custom chemical synthesis of the compounds used in our product candidates such as spiro-beta lactam. We cannot ensure that our suppliers will remain in business, have sufficient capacity or supply to meet our needs, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of single-source suppliers of raw materials,

components, key processes, and finished goods exposes us to several risks, including disruptions in supply, price increases, or late deliveries. There are, in general, relatively few alternative sources of supply for substitute components. In particular, given our use of the compound spiro-beta lactam, Sai will need to comply with certain regulatory and contractual requirements which significantly limit our ability to find alternative sources of supply. There are a limited number of suppliers that have the requisite facilities that comply with the required regulatory standards, which may lead to a supply gap in the unexpected event that Sai is unable to provide our products. These new vendors may be unable or unwilling to meet our future demands for our clinical studies or commercial sale. Any disruption in supply from Sai or any other single-source supplier or service provider, including disruptions related to COVID-19, could lead to supply delays or interruptions which would damage our business, financial condition, results of operations, and prospects. If we have to switch to a replacement supplier, the manufacture and delivery of our compounds could be interrupted for an extended period, adversely affecting our business.

Establishing additional or replacement suppliers for the components or processes used in our product candidates, if required, may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. For example, the FDA could require additional supplemental data and clinical study data if we rely upon a new supplier for the compounds used in our product candidates. While we seek to maintain adequate inventory of the single-source components and materials used in our products, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, submission of manufacturing information and a satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where our product candidates are produced is required to assess compliance with cGMPs and assure that the facilities, methods, and controls are adequate to preserve the product candidates' identity, strength, quality, and purity. Such inspections may include inspection of the manufacturers of the individual components of our process, which include the manufacturing processes and facilities of our single-source suppliers. Our current single-source suppliers have not undergone this process, nor have they had any components included in any product approved by the FDA.

Our reliance on single-source suppliers subjects us to a number of risks that could harm our reputation, business, and financial condition, including, among other things:

- delays to the development timelines for our product candidates;
- interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- delay in delivery due to our suppliers prioritizing other customer orders over ours;

- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, costs could significantly increase and our ability to meet demand for our products could be impacted.

Risks related to our intellectual property rights

If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our product candidates, others could compete against us more directly by developing and commercializing products similar or identical to ours, which would have a material adverse impact on our business, results of operations, financial condition, and prospects.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection in the United States and other countries for commercially important technology, inventions, and know-how related to our business, defend and enforce our patents, should they issue, preserve the confidentiality of our trade secrets, and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking patents intended to cover our products and compositions, their methods of use, and any other inventions that are important to the development of our business. Our owned patents and patent applications relate to NYX-2925, NYX-783, NYX-458, and other NMDAr modulators. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We cannot provide any assurances that any of our pending patent applications will mature into issued patents in any particular jurisdiction and, if they do, that such patents will include claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. The patent application and approval process is expensive, complex, 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. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. If we are unable to obtain or maintain patent protection with respect to any of our proprietary products and technology we develop, our business, financial condition, results of operations, and prospects could be materially harmed.

The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, which in recent years have been the subject of much litigation, and, therefore, the issuance, scope, validity, enforceability, and commercial value of any patent claims that we may obtain cannot be predicted with certainty. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of some foreign countries do not protect our proprietary rights to the same extent as the laws of the United States, and we may encounter significant problems in protecting our proprietary rights in these countries.

Obtaining and enforcing patents in the biotechnology and pharmaceutical indusies involve both technological and legal complexity, and is therefore costly, time-consuming, and inherently uncertain. In addition, the United States has enacted and implemented wide-ranging patent form legislation: the Leahy-Smith America Invents Act. The America Ivents Act also includes provisions that affect the way patent applications will be prosecuted and that may also affect patet litigation. It is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the

prosecution of our patent applications and the enforcement or defense of any patents that may issue from oupatent applications, all of which could have a material adverse effect on our business and financial condition.

Patent applications are generally maintained in confidence until publication. In the United States, for example, patent applications are typically maintained in secrecy for up to 18 months after their filing. Similarly, publication of discoveries in scientific or patent literature often lags behind actual discoveries. Consequently, we cannot be certain that we were the first to file patent applications on our product candidates. There is also no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which could be used by a third party to challenge the validity of our patents, should they issue, or prevent a patent from issuing from a pending patent application. Any of the foregoing could harm our competitive position, business, financial condition, results of operations, and prospects.

Moreover, our patents, if issued, may be challenged, deemed unenforceable, invalidated, or circumvented in the United States and abroad. U.S. patents and patent applications may also be subject to interference, derivation, *ex parte* reexamination, post-grant review, or *inter partes* review proceedings, supplemental examination and challenges in district court. Patents may also be subjected to opposition, post-grant review, or comparable proceedings lodged in various foreign, both national and regional, patent offices or courts. An adverse determination in any such proceeding could result in either loss of the patent or denial of the patent application, or loss or reduction in the scope of one or more of the claims of the patent or patent application, 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, such proceedings may be costly. Thus, any patents, should they issue, that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market, or otherwise commercialize our product candidates.

Furthermore, though a patent, if it were to issue, is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Even if a patent issues and is held to be valid and enforceable, competitors may be able to design around or circumvent our patents, such as using pre-existing or newly developed technology or products in a non-infringing manner. Other parties may develop and obtain patent protection for more effective technologies, designs, or methods. If these developments were to occur, they could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Our ability to enforce our patent rights depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or potential competitor's product. Any litigation to enforce or defend our patent rights, even if we were to prevail, could be costly and time-consuming and would divert the attention of our management and key personnel from our business operations. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend our patents, if and when issued, could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents, if and when issued, covering our product candidates are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered our product candidates, our financial position and results of operations would also be materially and adversely impacted.

We will incur significant ongoing expenses in maintaining our patent portfolio. Should we lack the funds to maintain our patent portfolio or to enforce our rights against infringers, we could be adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our pending patent applications, if issued, will include claims having a scope sufficient to protect our product candidates or any other products or product candidates;
- any of our pending patent applications will issue as patents at all;
- we will be able to successfully commercialize our product candidates, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- others will not use pre-existing technology to effectively compete against us;
- any of our patents, if issued, will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- that our commercial activities or products will not infringe upon the patents or proprietary rights of others.

Moreover, some of our future owned and licensed patents may be co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owner's interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us.

If we breach any of the agreements under which we license rights, we could lose license rights that are important to our business. For example, in connection with Allergan's acquisition of Naurex, we entered into a license agreement with Allergan, pursuant to which, among other things, Allergan granted us a non-exclusive license to certain intellectual property rights retained by Allergan in connection with such acquisition. In addition, we are party to a sublicense agreement with Allergan, pursuant to which Allergan granted us a sublicense for certain intellectual property rights that Allergan licenses from Northwestern. We may also need to obtain additional licenses to advance the development and commercialization of other product candidates we may develop. Our existing sublicense agreement with Northwestern imposes, and we expect that future license agreements will impose upon us various development and commercial diligence obligations, payment of milestones and/or royalties and other obligations. If we fail to comply with our obligations under certain of these agreements, we may be liable for damages, and the licensor may have the right to terminate the license, in which event we would not be able to develop, market, or otherwise commercialize products covered by the license. Our business could suffer, for example, if any current or future licenses terminate, if the licensors fail to abide by the terms of the license, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position may be harmed.

We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. Additionally, we rely on unpatented know-how, continuing technological innovation to develop, strengthen, and maintain the proprietary and competitive position of our product candidates, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. However, trade secrets are difficult to protect. For example, we may be required to share our trade secrets with third-party licensees, collaborators, consultants, contractors, or other advisors and we have limited control over the protection of trade secrets used by such third parties. Although we use reasonable efforts to protect our trade secrets, including by entering into confidentiality agreements, our employees, consultants, contractors, outside scientific collaborators, and other advisors may unintentionally or willfully disclose our trade secrets and proprietary information to competitors, and we may not have adequate remedies for any such disclosure. Enforcing a claim that a third party illegally obtained and used, disclosed, or misappropriated any of our trade secrets is difficult, expensive, and time-consuming, and the outcome is unpredictable. Furthermore, we may not obtain these agreements in all circumstances, and the employees and consultants who are parties to these agreements may breach or violate the terms of these agreements, thus we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. In addition, trade secret laws in the United States vary, and some U.S. courts as well as courts outside the United States are sometimes less willing or unwilling to protect trade secrets. Moreover, it is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Further, our trade secrets could otherwise become known or be independently discovered by our competitors or other third parties. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, vendors, former employees, and current employees. If our trade secrets or confidential or proprietary information is divulged to or acquired by third parties, including our competitors, our competitive position in the marketplace, business, financial condition, results of operations, and prospects may be materially adversely affected.

We may be sued for infringing the intellectual property rights of others, which may be costly and time-consuming and may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our product candidates, if approved.

Our success will depend in part on our ability to operate without infringing, misappropriating, or otherwise violating the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products, and methods do not or will not infringe the patents or other intellectual property rights of third parties. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technologies we use in our business.

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that our product candidates or the use of our technologies infringes or otherwise violates patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. As we continue to develop and, if approved, commercialize our current product candidates and future product candidates, competitors may claim that our technology infringes their intellectual property rights as part of business strategies designed to impede our successful commercialization. There may be third-party patents or patent applications with claims to compositions, materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because patent claims can be revised before issuance, third parties may have currently pending patent applications which may later result in issued patents that our product candidates may infringe, or which such third parties claim are infringed by our technologies. If a patent holder believes one or more of our product candidates infringes its patent rights, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are 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. 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 have a material adverse effect on our business and results of operations. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were to obtain a license, it could be granted on non-exclusive terms, thereby providing our competitors and other third parties access to the same technologies licensed to us. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our product candidates. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. There could also be public announcements of the results of the hearing, motions, or other interim proceedings or developments and if securities analysts or investors perceive those results to be negative, it could cause the price of shares of our common stock to decline. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action, or challenge the validity of the patents in court, or redesign our products. Patent litigation is costly and time-consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, intellectual property litigation or claims could force us to do one or more of the following:

- cease developing, selling or otherwise commercializing our product candidates;
- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and
- in the case of trademark claims, redesign, or rename, some or all of our product candidates to avoid infringing the intellectual property rights of third parties, which may not be possible and, even if possible, could be costly and time-consuming.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition, and prospects.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We enter into confidentiality and intellectual property assignment agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. The assignment of intellectual property rights under these agreements may not be automatic upon the creation of the intellectual property or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. For example, even if we have a consulting agreement in place with an academic advisor pursuant to which such academic advisor is required to assign any inventions developed in connection with providing services to us, such academic

advisor may not have the right to assign such inventions to us, as it may conflict with his or her obligations to assign all such intellectual property to his or her employing institution.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our 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 government fees on our owned patents and patent applications are or will be due to be paid to the U.S. Patent and Trademark Office, or USPTO, in several stages and various government patent agencies outside of the United States over the lifetime of such patents and patent applications and any patent rights we may own or license in the future. We have systems in place to remind us to pay these fees, and we employ outside firms to remind us or our licensors to pay annuity fees due to foreign governmental patent agencies on our foreign patents and pending foreign patent applications. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions over the lifetime of our owned patents and applications. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors or other third parties might be able to enter the market earlier than would otherwise have been the case and this circumstance could have a material adverse effect on our business, financial condition, results of operations, and prospects.

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

Even if our patent applications are issued, competitors and other third parties may infringe, misappropriate, or otherwise violate our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the attention of our management and key personnel from our business operations. Furthermore, many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. Our ability to enforce our patent rights also depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or potential competitor's product.

In an infringement proceeding, a court may disagree with our allegations and refuse to stop the other party from using the technology at issue on the grounds that our patents are not infringed by the technology in question, or may decide that a patent of ours is invalid, or unenforceable. An adverse result in any litigation, defense or post-grant proceedings could result in one or more of our patents being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing. If any of our patents, if and when issued, covering our product candidates are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our involvement in litigation or interference proceedings may fail and, even if successful, may result in substantial costs, and distract our management and other employees. We may not be able to prevent infringement, misappropriation of, or other violations of our

intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

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 this type of 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 have a material adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged.

If we initiated legal proceedings against a third party to enforce a patent, if and when issued, covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. The outcome of any such proceeding is generally unpredictable.

In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions of a patent include allegations that someone connected with prosecution of the patent application that matured into the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution of the patent application. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, *inter partes* review, post grant review and equivalent proceedings in foreign jurisdictions, e.g., opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

Additionally, changes in U.S. patent law could make it more likely that we lose patent protection, thereby impairing our ability to protect our products. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce any patents that may issue in the future.

We may not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing and prosecuting patent applications, and defending patents on product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States, assuming that rights are obtained in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. In addition, the statutory deadlines for pursuing patent protection in individual foreign jurisdictions are based on the priority date of each of our patent applications and we may not timely file foreign patent applications. For many of the patent families that we own, the relevant statutory deadlines have not yet expired. Thus, for each of these patent families, we will need to decide whether and where to pursue protection

outside the United States. For patent families relating to NYX-2925 and NYX-783 and to NYX-458, we have chosen to pursue patent protection in only the United States, Mexico, Canada, and certain jurisdictions in Europe, Asia, Australia, and South America

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology or pharmaceuticals. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of or marketing of competing products in violation 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. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

If we do not obtain additional protection under the Hatch-Waxman Act and similar foreign legislation by extending the patent terms and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional patent application filing date in its chain of priority. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive products, including generic products. Given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours.

Depending upon the timing, duration, and specifics of FDA marketing approval of our product candidates, one or more of the U.S. patents we own may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent term extension of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain a patent term extension or the term of any such extension is less than we request, the duration of patent protection we obtain for our product candidates may not provide us with any meaningful

commercial or competitive advantage, our competitors may obtain approval of competing products earlier than they would otherwise be able to do so, and our ability to generate revenues could be materially adversely affected.

We may be subject to damages resulting from claims that we or our employees, consultants, or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers.

Our employees have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We also engage advisors and consultants who are concurrently employed at universities or who perform services for other entities.

Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, and although we are not aware of any claims currently pending against us, we may be subject to claims that we or our employees, advisors, or consultants have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third party. We have and may in the future also be subject to claims that an employee, advisor, or consultant performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our product candidates, which would materially adversely affect our commercial development efforts.

Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to develop and/or practice technology that is similar to our technology or aspects of our technology but that is not covered by the claims of patents, should such patents issue from our patent applications;
- we might not have been the first to make the inventions covered by a pending patent application that we own;
- we might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;
- patents, if issued, that we own or license may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;
- we may not be able to obtain and/or maintain necessary or useful licenses on reasonable terms or at all;

- third parties may assert an ownership interest in our intellectual property and, if successful, such disputes may preclude us from exercising exclusive rights over that intellectual property;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business and results of operations.

General company-related risks

We may need to expand our company, and we may encounter difficulties in managing our ongoing development and potential expansion, which could disrupt our operations.

As of March 15, 2021, we had 34 full-time employees and no part-time employees. If any of our product candidates are submitted for or receive marketing approval, we may experience significant growth in the number of our employees and the scope of our operations. To manage our ongoing development and potential expansion, we must continue to implement and improve our managerial, operational, and financial systems, maintain or expand our facilities, and recruit and train additional qualified personnel. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train qualified personnel. This 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. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

Our future success depends on our ability to retain our management team and to attract, retain, and motivate qualified personnel.

Our ability to compete in the highly competitive biotechnology and biopharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific, and medical personnel. In order to induce valuable employees to continue their employment with us, we have provided stock options that vest over time. The value to employees of stock options that vest over time is significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. For instance, as a result of recent declines in our stock price, we have implemented retention measures intended to incentivize employees to continue their employment with us. However, we can provide no assurances that our retention measures will succeed in this objective, including if our stock price continues to decline.

We are highly dependent on our management, scientific and medical personnel, including our Chief Executive Officer, Norbert G. Riedel, Ph.D and our President and Chief Operating Officer, Andy Kidd, M.D. Despite our efforts to retain valuable employees, members of our management, scientific, and development teams may terminate their employment with us on short notice. The loss of the services of any of our executive officers, including Dr. Riedel, other key employees and other scientific and medical advisors, and an inability to find suitable replacements could result in delays in product development and harm our business. Pursuant to their employment arrangements, each of our executive officers, and other employees may voluntarily terminate their employment at any time, with or without notice. Our success also depends on our ability to continue to attract, retain, and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior scientific and medical personnel.

We may not be able to attract or retain qualified management and scientific personnel in the future due to the intense competition for a limited number of qualified personnel among biopharmaceutical, biotechnology, pharmaceutical, and

other businesses. Many of the other pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles, and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than what we may be able to offer. We also experience competition for the hiring of scientific personnel from universities and research institutions. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize product candidates will be limited.

We face potential product liability exposure, and, if claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical studies and the sale of our product candidates, if approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, or others selling or otherwise coming into contact with our product candidates. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing, or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of subjects from our clinical studies;
- substantial monetary awards to patients or other claimants;
- decreased demand for our product candidates or any future product candidates following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA warnings on product labels;
- litigation costs;
- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize our product candidates or any future product candidates, if approved.

We maintain product liability insurance coverage for our clinical studies with a $10.0 million annual aggregate coverage limit**.** Nevertheless, our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may not be able to obtain this product liability insurance on commercially reasonable terms. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business, and prospects could be materially adversely affected.

We incur significant costs as a result of operating as a public company, and our management team is required to devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting, and other expenses that we did not incur as a private company and these costs will further increase if and once we are no longer an "emerging growth company." In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and rules subsequently implemented by the SEC and The Nasdaq Stock Market have imposed 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 a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an "emerging growth company," we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are and will 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 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 that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Additionally, we may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls over financial reporting, we may not be able to produce timely and accurate financial statements. If that were to happen, our investors could lose confidence in our reported financial information, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities.

In order to satisfy our obligations as a public company, we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

As a public company, we need to establish and maintain effective disclosure and financial controls and make changes in our corporate governance practices. If we were to move out of an "emerging growth company", we will need to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge, and it may be difficult to recruit and maintain such personnel. Even if we are able to hire appropriate personnel, our existing operating expenses and operations will be impacted by the direct costs of their employment and the indirect consequences related to the diversion of management resources from product development efforts.

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, the

Tax Cuts and Jobs Act, or the TCJA, was enacted in 2017 and significantly reformed the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses generated after December 31, 2017 (though any such net operating losses may be carried forward indefinitely), and the modification or repeal of many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs"). 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 the TCJA and other changes in tax laws on an investment in our common stock.

Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

As of December 31, 2020, we had federal and state net operating loss, or NOL, carryforwards of $186.5 million and $17.7 million, respectively. Of the $186.5 million federal NOL carryforwards, $184.8 million of gross NOLs are limited under Sec. 382 of the Internal Revenue Code of 1986 ("Section 382"), of which $48.9 million gross NOLs were generated prior to 2018 and will begin to expire in 2035, and the remainder were generated after 2018 and have an indefinite carryforward period. All the gross NOLs that are limited are subject to a substantial annual limitation, and $33.3 million will expire based on such limitations. Under Section 382, changes in our ownership may limit the amount of our NOL carryforwards and research and development tax credit carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation may significantly reduce our ability to utilize NOL carryforwards and research and development tax credit carryforwards before they expire. During 2020, we performed a detailed analysis of historical and current Section 382 ownership changes that may limit the utilization of NOL carryforwards. Except for approximately $184.8 million of NOLs arising prior to our October 2020 secondary offering, we expect the entire remaining federal NOL carryforward will not be subject to limitations under Section 382. However, sales of our common stock by our existing stockholders, or additional sales of our common stock by us, could trigger additional limitations under Section 382 and have a material adverse effect on our results of operations in future years.

Unfavorable global economic conditions could adversely affect our business, financial condition, or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets, including any recession, depression or other sustained adverse market event resulting from the spread of COVID-19. A global financial crisis can cause extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the global financial crisis years ago, could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We, or the third parties upon whom we depend, may be adversely affected by earthquakes or other natural disasters or pandemics, including COVID-19, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters or pandemics, including COVID-19, could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition, and prospects. If a natural disaster, power outage, or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers and suppliers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for

us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Our internal computer systems, or those of our third-party CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates' development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunication and electrical failures. While we have not experienced any such system failure, accident, or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical study data for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company and our contractors or consultants. In addition, outside parties may attempt to penetrate our systems or those of our contractors or consultants or fraudulently induce our personnel or the personnel of our contractors or consultants to disclose sensitive information in order to gain access to our data and/or systems. We have experienced a number of unsuccessful phishing attacks on our systems, and we may continue to experience threats to our data and systems, including malicious codes and viruses, phishing and other cyber-attacks. The number and complexity of these threats continue to increase over time, including as a result of employees working remotely in response to COVID-19. If a material breach of our information technology systems or those of our contractors or consultants occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive practices. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. In addition, there can be no assurance that our internal information technology systems or those of our third-party contractors, or our consultants' efforts to implement adequate security and control measures, will be sufficient to protect us against breakdowns, service disruption, data deterioration or loss in the event of a system malfunction, or prevent data from being stolen or corrupted in the event of a cyberattack, security breach, industrial espionage attacks or insider threat attacks which could result in financial, legal, business or reputational harm.

We may acquire businesses or products, or form strategic alliances, in the future, and we may not realize the benefits of such acquisitions.

We may acquire additional businesses or products, form strategic alliances, or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing, and marketing any new products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot provide assurance that, following any such acquisition, we will achieve the synergies expected in order to justify the transaction.

Risks related to our common stock

An active trading market for our common stock may not be sustained, and you may not be able to resell your shares at or above the public offering price.

Prior to our IPO in June 2018, there had been no public market for our common stock. Although our common stock is listed on The Nasdaq Global Select Market, an active trading market for our shares may never be sustained. If an active market for our common stock is not sustained, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at or above the prices at which they acquired their shares or sell their shares at the time they would like to sell. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

Market volatility may affect our stock price and the value of your investment.

The market price for our common stock has been, and is likely to continue to be, volatile for the foreseeable future, in part because our common stock had not been previously traded publicly prior to our IPO. For example, in the year ended December 31, 2020, our common stock's sales price on The Nasdaq Global Select Market ranged from a low of $1.60 to a high of $6.47. The market price of our common stock may fluctuate significantly in response to a number of factors, most of which we cannot control.

In recent years, the stock market in general, and the market for pharmaceutical and biotechnology companies in particular, has experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to changes in the operating performance of the companies whose stock is experiencing those price and volume fluctuations. Broad market and industry factors may seriously affect the market price of our common stock, regardless of our actual operating performance. Following periods of such volatility in the market price of a company's securities, securities class action litigation has often been brought against that company. Because of the potential volatility of our stock price, we may become the target of securities litigation in the future. Securities litigation could result in substantial costs and divert management's attention and resources from our business.

Our principal stockholders and management own a significant percentage of our stock and, if they choose to act together, will be able to control or exercise significant influence over matters subject to stockholder approval, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control.

Based on 66,889,625 shares outstanding as of March 15, 2021, our executive officers, directors, five percent stockholders and their affiliates beneficially owned approximately 47% of our voting stock. The existing holdings of our executive officers, directors, principal stockholders, and their affiliates, including investment funds affiliated with Bain Capital Life Sciences, Adams Street, and Longitude represent beneficial ownership, in the aggregate, of approximately 38% of our outstanding common stock. As a result, these stockholders, if they act together, will be able to influence our management and affairs and control the outcome of matters submitted to our stockholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

- delaying, deferring, or preventing a change of control of us;
- impeding a merger, consolidation, takeover, or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

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

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline. We have filed a registration statement on Form S-8 under the Securities Act to register shares issued or reserved for issuance under our equity incentive plans and will file additional registration statements on Form S-8 to register additional shares pursuant to the "evergreen" provisions under our equity incentive plans. These shares are eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act.

In addition, as of March 15, 2021, the holders of approximately 8,401,404 shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the market our common stock.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, even one that may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include a classified board of directors, a prohibition on actions by written consent of our stockholders, and the ability of our board of directors to issue preferred stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirers to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, 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, which is responsible for appointing the members of our management.

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 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 or proceeding brought on our behalf; (2) any action asserting a claim of or based on a breach of a fiduciary duty owed by any of our current or former directors, officers or other employees to us or our stockholders; (3) any action asserting a claim against us or any of our current or former directors, officers, employees or stockholders arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or (4) any action asserting a claim governed by the internal affairs doctrine, or the Delaware Forum Provision. The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act or the Exchange Act. Our amended and restated bylaws further provide that, unless we consent in writing to an alternative forum, the United States District Court for the Northern District of Illinois will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision. We have chosen the United States District Court for the Northern District of Illinois as the exclusive forum for such Securities Act causes of action because our principal executive offices are located in Evanston, Illinois. In addition, our amended and restated 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 foregoing Delaware Forum Provision and the Federal Forum Provision.

We recognize that the Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders who assert the provision is not enforceable 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 or the

State of Illinois. Additionally, these forum selection clauses in our amended and restated 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. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert the provision is not enforceable or invalid. The Court of Chancery of the State of Delaware and the United States District Court for the Northern District of Illinois 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.

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

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company until December 31, 2023, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th or if we have annual gross revenues of $1.07 billion or more in any fiscal year, we would cease to be an emerging growth company as of December 31 of the applicable year. We also would cease to be an emerging growth company if we issue more than $1 billion of non-convertible debt over a three-year period.

We are also a "smaller reporting company," as defined in Rule 12b-2 under the Securities Exchange Act of 1934, as amended. We would cease to be a smaller reporting company if we have a public float in excess of $250 million, or have annual revenues in excess of $100 million and a public float in excess of $700 million, determined on an annual basis.

As an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

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

In addition to the above reduced disclosure requirements applicable to emerging growth companies, as a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not smaller reporting companies. These exemptions include:

- being permitted to provide only two years of audited financial statements in this Annual Report on Form 10-K, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure; and
- not being required to furnish a stock performance graph in our annual report.

We cannot predict whether investors will find our common stock less attractive as a result of our reliance on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

We do not intend to pay dividends on our common stock and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our common stock.

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation, and expansion of our business, and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

If securities or industry analysts do not publish or cease publishing research or reports or publish misleading, inaccurate, or unfavorable research about us, our business or our market, our stock price, and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that securities or industry analysts publish about us, our business, our market, or our competitors. If one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, or provides more favorable relative recommendations about our competitors, our stock price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, demand for our stock could decrease, which could cause our stock price or trading volume to decline.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We currently have two locations located in Evanston, Illinois where we lease space. Our research facilities, which include laboratories and office space, consists of approximately 4,700 square feet and are leased through Northwestern University. We lease a facility containing our research and development, laboratory and office space, which consists of approximately 16,519 square feet located at 909 Davis Street, Suite 600, Evanston, IL 60201. Our lease on our corporate headquarters expires on August 31, 2022 and is subject to a five-year renewal period in accordance with the terms of the lease.

We believe our facilities are adequate for our current needs and that suitable additional substitute space would be available if needed.

Item 3. Legal Proceedings.

We are not a party to any legal proceedings, and we are not aware of any material claims or actions pending or threatened against us. In the future, we might from time to time become involved in litigation relating to claims arising from our ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

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.

Our common stock trades on The Nasdaq Global Select Market under the symbol "APTX". Trading of our common stock commenced on June 21, 2018, in connection with our initial public offering, or IPO. Prior to that time, there was no established public trading market for our common stock.

As of March 15, 2021, we had approximately 125 holders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and growth of our business. We do not expect to pay any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects, then applicable contractual restrictions and any other factors deemed relevant by our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Equity Compensation Plan

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 on Form 10-K.

Use of Proceeds from the Initial Public Offering

On June 25, 2018, we closed our initial public offering, or IPO, in which we issued and sold 6,399,999 shares of common stock at a public offering price of $16.00 per share, and issued an additional 959,999 shares of common stock at a price of $16.00 per share pursuant to the exercise of the underwriters' over-allotment option. All of the shares of common stock issued and sold in our initial public offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (Registration No. 333-225150), which was declared effective by the SEC on June 20, 2018. J.P. Morgan, Cowen, Leerink Partners, and BMO Capital Markets acted as joint book-running managers for the offering. The aggregate gross proceeds to us from our initial public offering, inclusive of the over-allotment exercise, were $117.8 million.

The aggregate net proceeds to us from the public offering, inclusive of the over-allotment exercise, were approximately $106.5 million, after deducting underwriting discounts and commissions and other offering expenses payable by us of approximately $3.0 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliate.

As described in the final prospectus for the IPO filed with the SEC pursuant to Rule 424(b)(4) dated June 20, 2018, we expect to use the net proceeds from our IPO to fund our ongoing clinical development of NYX-2925, to advance NYX-783 through completion of our Phase 2 clinical study, to advance NYX-458 for the treatment of Parkinson's disease cognitive impairment through completion of Phase 1 clinical development and into our planned Phase 2 clinical study, and to explore NMDAr-dependent biomarkers and develop any additional product candidates.

Information related to use of proceeds from registered securities is incorporated herein by reference to the "Use of Proceeds" section of the Company's final prospectus related to the IPO. There has been no material change in the planned use of proceeds from our IPO as described in our final prospectus.

Item 6. Selected Financial Data.

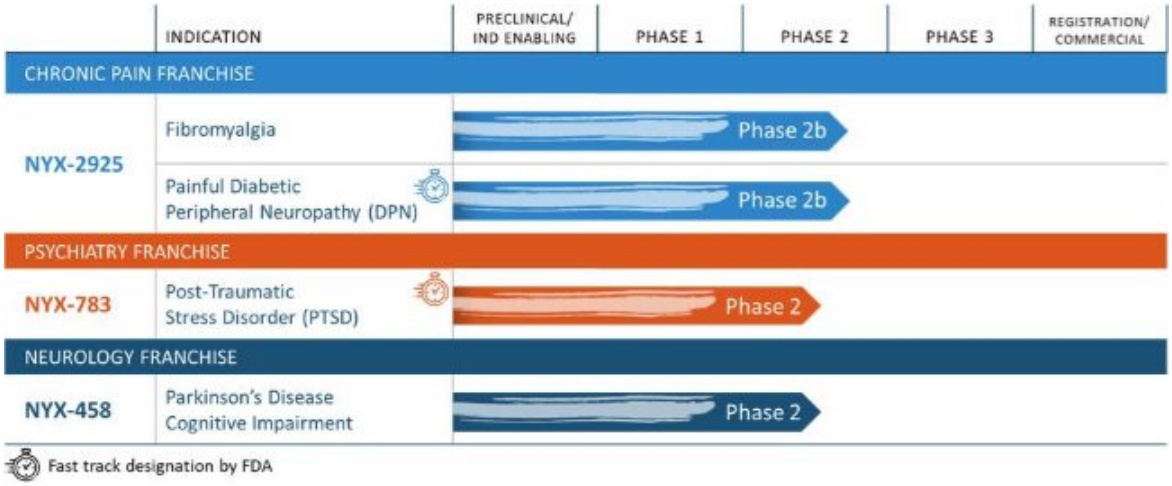
Information requested by this Item is not applicable as we are electing scaled disclosure requirements available to Smaller Reporting Companies with respect to this Item.

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 financial statements and related notes included elsewhere in 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 our plans, objectives, expectations, intentions and beliefs. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified below and those discussed in the section entitled "Risk Factors" included elsewhere in this Annual Report on Form 10-K.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel, proprietary, synthetic small molecules for the treatment of brain and nervous system disorders. We focus our efforts on targeting and modulating N-methyl-D-aspartate receptors, or NMDArs, which are vital to normal and effective function of the brain and nervous system. We believe leveraging the therapeutic advantages of the differentiated modulatory mechanism of our compounds will drive a paradigm shift in the treatment of disorders of the brain and nervous system. We are advancing a pipeline of distinct product candidates derived from our NMDAr modulator discovery platform, or the discovery platform. The following table summarizes the current status of our development programs as of the date of this annual report.



NYX-2925 is in clinical development for the treatment of chronic pain. NYX-2925 is being evaluated in two Phase 2b studies in two chronic pain conditions: one evaluating the efficacy and safety in approximately 200 patients with painful diabetic peripheral neuropathy, or painful DPN, and the other evaluating the efficacy and safety in approximately 300 patients with fibromyalgia. These studies have both recently recommenced enrollment following their temporary suspension in March of 2020 due to challenges introduced by the COVID-19 pandemic. NYX-783 is in clinical development for the treatment of post-traumatic stress disorder, or PTSD. We recently completed an initial exploratory Phase 2 study to evaluate safety, tolerability, and signals of efficacy of NYX-783 in 160 patients with PTSD. In the study, patients treated with NYX-783 demonstrated improvements across PTSD symptoms and NYX-783 was well-tolerated with no drug-related serious adverse events reported. The NYX-783 50 mg group demonstrated a clinically meaningful improvement from baseline on CAPS-5 Total score after 4 weeks of treatment and, while the exploratory study was powered based on clinical, and not statistical, considerations, on some measures NYX-783 did demonstrate statistically significant separation from placebo. NYX-458 is in Phase 2 clinical development for the treatment of cognitive impairment associated with Parkinson's disease and dementia with Lewy bodies. We recently recommenced study activities, including site initiation and obtaining IRB approval, for a Phase 2 exploratory study that was

temporarily suspended in March of 2020 due to challenges introduced by the COVID-19 pandemic. We expect to recommence the screening and enrollment of patients in that study following an investigator meeting that is planned for March 26, 2021.

We do not expect to generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for a product candidate, which we expect will take a number of years and the outcome of which is uncertain, or enter into collaborative agreements with third parties, the timing of which is largely beyond our control and may never occur. To fund our current and future operating plans, we will need additional capital, which we may obtain through one or more equity offerings, debt financings, or other third-party funding, including potential strategic alliances and licensing or collaboration arrangements. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all, including as a result of COVID-19. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our current product candidates, or any additional product candidates, if developed. The amount and timing of our future funding requirements will depend on many factors, including the impacts of COVID-19, our ability to successfully enroll subjects in a timely way for the clinical studies, and the pace and results of our preclinical and clinical development efforts. We cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

The COVID-19 pandemic has and could further adversely impact our clinical and/or preclinical studies, as well as our business operations. We continue to evaluate the impact of the COVID-19 pandemic on patients and our employees, as well as our operations and the operations of our business partners and healthcare communities. In response to the COVID-19 pandemic, we have implemented policies to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory or manufacturing facility, a work-from-home policy applicable to the majority of our personnel, and a phased approach to bringing personnel back to our locations over time. However, the ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments which are difficult to predict.

Financial operations overview

Revenues

We have not generated any revenue from product sales. We are unable to predict when, if ever, material net cash inflows will commence from sales of our products, if approved. Our revenue to date has been primarily derived from a research collaboration agreement with Allergan (now a subsidiary of AbbVie), under which the jointly funded research activities and associated payments by Allergan to us concluded in the third quarter of 2020; a development services agreement with Allergan, which was put in place to continue certain development activities for a pre-determined period of time following Allergan's acquisition of Naurex Inc.; and research and development grants from the U.S. government that have no repayment or royalty obligations and none of which are currently outstanding.

Operating expenses

Research and development expenses

Research and development activities account for a significant portion of our operating expenses. We expense research and development costs as incurred. Research and development expense consists of costs incurred in connection with the development of our product candidates, including:

- fees paid to consultants, sponsored researchers, contract manufacturing organizations, or CMOs, and contract research organizations, or CROs, including in connection with our preclinical and clinical studies, and other related clinical study fees, such as for investigator grants, patient screening, laboratory work, clinical study database management, and statistical compilation and analysis;

- costs related to acquiring and maintaining preclinical and clinical study materials and facilities;

- costs related to compliance with regulatory requirements; and
- costs related to salaries, bonuses, and other compensation for employees in research and development functions.

At this time, we cannot reasonably estimate or know the nature, timing, and costs of the efforts that will be necessary to complete the development of our product candidates. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty related to:

- the impacts of COVID-19;
- future clinical study results; the scope, rate of progress, and expense of our ongoing as well as any additional preclinical studies, clinical studies and other research and development activities;
- clinical study enrollment rate or design;
- the manufacturing of our product candidates;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- significant and changing government regulation;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers, developing and timely delivery of commercial-grade drug formulations that can be used in our clinical trials and for commercial launch;
- the timing and receipt of regulatory approvals, if any; and
- the risks disclosed in the section entitled “Risk Factors” of this Annual Report on Form 10-K.

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, timing, and viability associated with the development of that product candidate.

We expect our research and development expenses to increase over the next several years as we continue to implement our business strategy, which includes advancing our product candidates into and through clinical development, expanding our research and development efforts, seeking regulatory approvals for any product candidates for which we successfully complete clinical studies, accessing and developing additional product candidates, and hiring additional personnel to support our research and development efforts. In addition, product candidates in later stages of clinical development generally incur higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical studies. As such, we expect our research and development expenses to increase as our product candidates advance into later stages of clinical development.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation. General and administrative expenses also include rent as well as professional fees for legal, consulting, accounting, and audit services.

In the future, we expect that our general and administrative expenses will increase as we continue to support our research and development and the potential commercialization of our product candidates, if approved. We also anticipate that we will incur increased accounting, audit, legal, tax, regulatory, compliance, and director and officer insurance costs, as well

as investor and public relations expenses associated with maintaining compliance with exchange listing and SEC requirements.

Other income

Other income consists of interest income earned on our cash and cash equivalents.

Results of operations

Comparison of years ended December 31, 2020 and 2019

The following table summarizes our results of operations for the years ended December 31, 2020 and 2019 (in thousands):

	Year ended December 31,		Increase (Decrease)
	2020	2019	
Revenues:			
Collaboration revenue	$ 1,564	$ 3,669	$ (2,105)
Operating expenses:			
Research and development	32,835	44,330	(11,495)
General and administrative	19,494	18,952	542
Total operating expenses	52,329	63,282	(10,953)
Loss from operations	(50,765)	(59,613)	(8,848)
Other income	712	2,203	(1,491)
Net loss and comprehensive loss	$ (50,053)	$ (57,410)	$ (7,357)

Collaboration revenue

Collaboration revenue was $1.6 million for the year ended December 31, 2020, compared to $3.7 million for the year ended December 31, 2019 and is attributable to the research collaboration with Allergan. The jointly funded research activities under the research collaboration and the associated payments by Allergan came to their contractual conclusion in the third quarter of 2020.

Research and development expenses

The following table summarizes our research and development expenses incurred during the years ended December 31, 2020 and 2019 (in thousands):

	Year ended December 31,		Increase (Decrease)
	2020	2019	
NYX-2925	$ 10,985	$ 11,304	$ (319)
NYX-783	6,690	8,001	(1,311)
NYX-458	3,367	6,009	(2,642)
Preclinical research and discovery programs	3,046	6,067	(3,021)
Personnel and related costs	8,747	12,949	(4,202)
Total research and development expenses	$ 32,835	$ 44,330	$ (11,495)

Research and development expenses were $32.8 million for the year ended December 31, 2020, compared to $44.3 million for the year ended December 31, 2019. The decrease of $11.5 million was primarily due to the following:

- approximately $4.2 million decrease due to lower employee headcount costs and related support costs in 2020 compared to 2019;

- approximately $3.0 million decrease for costs associated with our preclinical research efforts with external research organizations and in part by the natural conclusion of the research collaboration with Allergan in the third quarter of 2020;
- approximately $2.6 million decrease related to the ongoing development of NYX-458 for the treatment of Parkinson's disease cognitive impairment, including the temporary suspension of the exploratory Phase 2 study of NYX-458 due to the COVID-19 pandemic; and
- approximately $1.3 million decrease for clinical, regulatory, and drug product costs related to the ongoing development of NYX-783 due to the conclusion of the Phase 2 study in October 2020.

General and administrative expenses

General and administrative expenses were $19.5 million for the year ended December 31, 2020, compared to $19.0 million for the year ended December 31, 2019. The increase of $0.5 million was due to a $1.7 million increase related to employee non-cash stock based-compensation expenses, costs associated with being a public company, and insurance costs to support ongoing business operations offset by a decrease of $1.3 million related to reduced employee headcount, professional fees, and patent costs

Other income

We recorded $0.7 million of other income for the year ended December 31, 2020, compared to $2.2 million for the year ended December 31, 2019. This was due to decreased interest income earned on our cash and cash equivalents as a result of decreased interest rates during 2020 compared to 2019.

Liquidity and capital resources

From our inception through December 31, 2020, we have incurred significant operating losses and have funded our operations to date through proceeds from collaborations, grants, sales of convertible preferred stock, and our IPO and follow-on equity offerings. We have generated limited revenue to date from a research collaboration agreement with Allergan, a development services agreement with Allergan, and research and development grants from the U.S. government.

On June 25, 2018, we completed an initial public offering, pursuant to which we issued and sold 7,359,998 shares of our common stock at a price of $16.00 per share, which included 959,999 shares sold pursuant to the exercise of the underwriters' option to purchase additional shares. We received $106.5 million of proceeds, net of underwriting discounts and commissions and other offering expenses.

On July 1, 2019, we entered into a Sales Agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, pursuant to which we may issue and sell, from time to time, shares of our common stock having an aggregate offering price of up to $50.0 million through Cowen as sales agent. Cowen may sell common stock by any method permitted by law deemed to be an "at the market offering" as defined in Rule 415(a)(4) of the Securities Act, including sales made directly on or through the Nasdaq Global Select Market or any other existing trade market for the common stock, in negotiated transactions at market prices prevailing at the time of sale or at prices related to prevailing market prices, or any other method permitted by law. Cowen will be entitled to receive 3.0% of the gross sales price per share of common stock sold under the Sales Agreement. There were no shares issued in 2019. During the year ended December 31, 2020, 1,491,482 shares of common stock have been issued and sold pursuant to the Sales Agreement at a weighted-average price of $3.89 per share. During the year ended December 31, 2020, we received $5.7 million of net proceeds after deducting sales commissions and other offering expenses.

On January 14, 2020, we completed a follow-on public offering of our common stock pursuant to an effective registration statement on Form S-3. We sold an aggregate of 11,691,666 shares of common stock, which included the exercise in full of the underwriters' option to purchase additional shares, at a public offering price of $3.00 per share. Net proceeds from the offering were approximately $33.3 million after deducting underwriting discounts and commissions as well as other offering expenses.

On October 26, 2020, we completed a follow-on public offering of our common stock pursuant to an effective registration statement on Form S-3. We sold an aggregate of 16,100,000 shares of common stock, which included the exercise in full of the underwriters' option to purchase additional shares, at a public offering price of $3.00 per share. Net proceeds from the offering were approximately $45.1 million after deducting underwriting discounts and commissions as well as estimated offering expenses.

Subsequent to December 31, 2020 and through the filing date of this Annual Report on Form 10-K, we sold an aggregate of 3,629,458 shares under the "at the market offering" at an average price of $4.03 for net proceeds of $14.5 million.

As of December 31, 2020, we had cash and cash equivalents of $141.0 million. We invest our cash equivalents in liquid money market accounts

Funding requirements

Our primary uses of capital are, and we expect will continue to be, research and development services, compensation and related expenses, laboratory and related supplies, legal and other regulatory expenses, patent prosecution filing and maintenance costs for our licensed intellectual property and general overhead costs. We expect to continue to incur significant expenses and operating losses for the foreseeable future. In addition, since the closing of our IPO, we have incurred, and expect to incur, additional costs associated with operating as a public company. We anticipate that our expenses will increase significantly in connection with our ongoing activities, as we:

- seek to address and recover from impacts of COVID-19;
- advance the clinical development of our lead product candidates;
- continue to improve the manufacturing process for our product candidates; and manufacture clinical supplies as our development progresses;
- continue the research and development of our preclinical product candidates;
- seek to identify and develop additional product candidates;
- maintain, expand, and protect our intellectual property portfolio; and
- improve our operational, financial, and management systems to support our clinical development and other operations.

Outlook

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our cash and cash equivalents as of December 31, 2020 will be sufficient to fund our operations for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect.

We do not expect to generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for a product candidate, which we expect will take a number of years and the outcome of which is uncertain, or enter into collaborative agreements with third parties, the timing of which is largely beyond our control and may never occur. To fund our current and future operating plans, we will need additional capital, which we may obtain through one or more equity offerings, debt financings, or other third-party funding, including potential strategic alliances and licensing or collaboration arrangements. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all, including as a result of COVID-19. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our current product candidates, or any additional product candidates, if

developed. The amount and timing of our future funding requirements will depend on many factors, including the effects of COVID-19, our ability to successfully enroll subjects in a timely way for the clinical studies and the pace and results of our preclinical and clinical development efforts. We cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

Cash flows

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

	Year ended December 31,	
	2020	**2019**
Net cash provided by (used in):		
Operating activities	$ (42,356)	$ (52,087)
Investing activities	(214)	(39)
Financing activities	84,675	192
Net increase (decrease) in cash, cash equivalents and restricted cash	**$ 42,105**	**$ (51,934)**

Operating activities

For the year ended December 31, 2020, compared to the same period in 2019, the $9.7 million decrease in net cash used in operating activities was primarily due to a $7.4 million decrease in our net loss year over year, driven mostly by lower research and development expenses and and a use of cash decrease of $1.5 million due to changes in working capital largely driven by timing of cash paid to support our clinical research programs.

Investing activities

For the year ended December 31, 2020, compared to the same period in 2019, the $0.2 million increase in net cash used in investing activities was primarily due to purchases of lab equipment.

Financing activities

For the year ended December 31, 2020, compared to the same period in 2019, the $84.5 million increase in net cash provided by financing activities was primarily due to $78.5 million and $5.7 million of net proceeds received from our January and October 2020 follow-on public offerings and 2020 “at the market offering”, respectively, net of underwriting discounts and commissions and other offering expenses.

Critical accounting policies and significant judgments and estimates

We prepare our financial statements in accordance with generally accepted accounting principles in the United States, or U.S. GAAP. In the preparation of these financial statements, we are required to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and related disclosures. To the extent that there are material differences between these estimates and actual results, our financial condition or operating results would be affected. We base our estimates on past experience and other assumptions that we believe are reasonable under the circumstances, and we evaluate these estimates on an ongoing basis.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing in this Annual Report on Form 10-K, we believe the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

Research and development

As part of the process of preparing our financial statements, we are required to estimate certain of our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with

our personnel to identify services that have been performed on our behalf, and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with performing research and development services on our behalf;
- investigative sites or other providers in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to product manufacturing, development, and distribution of clinical supplies.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of patients, number of sites activated and level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting expenses that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of accrued or prepaid research and development expenses.

Stock-based compensation

We measure stock-based awards granted to our directors and employees at fair value on the date of grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. Generally, we issue stock options and restricted stock with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have historically granted stock options with exercise prices equivalent to the fair value of our common stock as of the date of grant.

The fair value of our common stock is determined based on the quoted market price of our common stock. Prior to our IPO, the estimates in determining our stock-based compensation valuations were highly complex and subjective, and since our stock was not publicly traded, our board of directors estimated the fair value of our common stock at various dates, with input from management, considering our then most recently available third-party valuations of common stock and its assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. The grant date fair value of our options is determined using the Black-Scholes option-pricing model. The expected term of our options has been determined utilizing the “simplified method” for awards that qualify as “plain-vanilla” options. The historical volatility of share values of publicly traded companies within the biotechnology industry are used as a surrogate for the expected volatility of our common stock. The determination of the set of guideline public companies used to determine the volality assumption continues to represent a significant estimate in the determination of the grant date fair value of our options. We have not made significant changes in the identification of these guideline public companies in recent years. As of yet, we have not incorporated our own historical share price volatility into this determination, and plan to continuously reevaluate this assumption as we develop more history. 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 we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future.

JOBS Act

Under Section 107(b) of the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, an "emerging growth company" can delay the adoption of new or revised accounting standards until such time as those standards would apply to private companies. We intend to avail of this exemption. There are other exemptions and reduced reporting requirements provided by the JOBS Act that we are currently evaluating. For example, as an "emerging growth company," we are exempt from Sections 14A(a) and (b) of the Exchange Act which would otherwise require us to (1) submit certain executive compensation matters to shareholder advisory votes, such as "say-on-pay," "say-on-frequency," and "golden parachutes;" and (2) disclose certain executive compensation related items such as the correlation between executive compensation and performance and comparisons of our chief executive officer's compensation to our median employee compensation. We also intend to avail of an exemption from the rule requiring us to provide an auditor's attestation report on our internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act. We will continue to remain an "emerging growth company" until the earliest of the following: (1) December 31, 2023; (2) the last day of the fiscal year in which our total annual gross revenue is equal to or more than $1.07 billion; (3) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (4) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

Recent accounting pronouncements

See Note 2 to our financial statements appearing in this Annual Report on Form 10-K for a full description of recent accounting pronouncements including the respective expected dates of adoption and estimated effects, if any, on our financial statements.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Information requested by this Item 7A. Quantitative and Qualitative Disclosures about Market Risk is not applicable as we are electing scaled disclosure requirements available to Smaller Reporting Companies with respect to this Item.

Item 8. Financial Statements and Supplementary Data.

Our financial statements, together with the report of our independent registered public accounting firm, appear in this Annual Report on Form 10-K beginning on page 104.

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

There has been no change of accountants nor any disagreements with accountants on any matter of accounting principles or practices or financial disclosure required to be reported under this Item.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

We have established disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) designed to ensure that information required to be disclosed in the reports that the 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 and is accumulated and communicated to management, including the principal executive officer (our Chief Executive Officer) and principal financial officer (our Chief Financial Officer), to allow timely decisions regarding required disclosure.

Management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. 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 cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on the evaluation of our disclosure controls and procedures as of December 31, 2020, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Internal Control Over Financial Reporting

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rule 13a-15(f) under the Securities Exchange Act of 1934, as amended. Our management conducted an assessment of the effectiveness of our internal control over financial reporting based on the criteria set forth in "Internal Control-Integrated Framework (2013)" issued by the Committee of Sponsoring Organization of the Treadway Commission. Based on this assessment, management concluded that, as of December 31, 2020, our internal control over financial reporting was effective.

This annual report does not include an attestation report of our independent registered public accounting firm on internal control over financial reporting due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting that occurred during the fiscal quarter ended December 31, 2020 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item regarding directors, executive officers and corporate governance will be included in our 2021 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this item regarding executive compensation will be included in our 2021 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, 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 regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2021 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

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

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2021 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this item regarding principal accounting fees and services will be included in our 2021 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a) The following documents are included in this Annual Report on Form 10-K:

1. The following Report and Financial Statements of the Company are included in this Annual Report:

   Report of Independent Registered Public Accounting Firm

   Balance Sheets

   Statements of Operations

   Statements of Stockholders' Equity

   Statements of Cash Flows

   Notes to Financial Statements

2. All financial schedules have been omitted because the required information is either presented in the financial statements or the notes thereto or is not applicable or required.

3. 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.

Deloitte.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Aptinyx Inc.

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Aptinyx Inc. (the "Company") as of December 31, 2020 and 2019, the related statements of operations and comprehensive loss, stockholders' equity, and cash flows, for each of the two years in the period ended December 31, 2020, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2020, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company’s internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the 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 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ **Deloitte & Touche LLP**

Chicago, Illinois
March 24, 2021

We have served as the Company's auditor since 2017.

Aptinyx Inc.

Balance Sheets
(In thousands, except per share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 141,028	$ 98,849
Restricted cash	179	179
Accounts receivable	257	444
Prepaid expenses and other current assets	8,140	5,637
Total current assets	149,604	105,109
Other assets	92	166
Property and equipment, net	910	1,204
Total assets	$ 150,606	$ 106,479
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,209	$ 1,555
Accrued expenses and other current liabilities	3,374	3,341
Total current liabilities	4,583	4,896
Other long-term liabilities	114	272
Total liabilities	$ 4,697	$ 5,168
Commitments and contingencies (see Note 15)		
Stockholders' equity:		
Preferred stock, $0.01 par value, 10,000 shares authorized and no shares issued and outstanding as of December 31, 2020 and December 31, 2019	—	—
Common stock, $0.01 par value, 150,000 shares authorized as of December 31, 2020 and December 31, 2019, 63,257 and 33,739 issued and outstanding as of December 31, 2020 and December 31, 2019	633	337
Additional paid-in capital	358,277	263,922
Accumulated deficit	(213,001)	(162,948)
Total stockholders' equity	$ 145,909	$ 101,311
Total liabilities and stockholders' equity	$ 150,606	$ 106,479

See accompanying notes to financial statements.

Aptinyx Inc.
Statements of Operations and Comprehensive Loss
(in thousands, except per share data)

	Year ended December 31,	
	2020	**2019**
Revenues:		
Collaboration revenue	$ 1,564	$ 3,669
Operating expenses:		
Research and development	32,835	44,330
General and administrative	19,494	18,952
Total operating expenses	52,329	63,282
Loss from operations	(50,765)	(59,613)
Other income	712	2,203
Net loss and comprehensive loss	$ (50,053)	$ (57,410)
Net loss per share attributable to common stockholders, basic and diluted	$ (1.02)	$ (1.71)
Weighted-average number of common shares outstanding, basic and diluted	48,866	33,556

See accompanying notes to financial statements.

Aptinyx Inc.
Statements of Stockholders' Equity

(in thousands)

	Shares	Common stock Amount	Additional paid-in capital	Accumulated deficit	Total stockholders' equity
Balance at January 1, 2019	33,341	$ 333	$ 254,516	$ (105,538)	$ 149,311
Issuance of common stock upon vesting of restricted stock	217	2	(2)	—	—
Stock-based compensation	—	—	9,036	—	9,036
Issuance of common stock upon exercise of stock options	181	2	372	—	374
Net loss	—	—	—	(57,410)	(57,410)
Balance at December 31, 2019	33,739	$ 337	$ 263,922	$ (162,948)	$ 101,311
Issuance of common stock upon vesting of restricted stock	23	1	(1)	—	—
Stock-based compensation	—	—	9,979	—	9,979
Issuance of common stock upon at the market offering, net of sales commissions and other offering costs of $274	1,491	15	5,690	—	5,705
Issuance of common stock upon public offering, net of underwriters' discount and other offering costs of $4,898	27,792	278	78,199	—	78,477
Issuance of common stock upon exercise of stock options	212	2	488	—	490
Net loss	—	—	—	(50,053)	(50,053)
Balance at December 31, 2020	63,257	$ 633	$ 358,277	$ (213,001)	$ 145,909

See accompanying notes to financial statements.

Aptinyx Inc.
Statements of Cash Flows
(in thousands)

	Year Ended December 31,	
	2020	**2019**
Cash flows from operating activities:		
Net loss	$ (50,053)	$ (57,410)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization expense	421	455
Loss on disposal of property and equipment	—	3
Stock-based compensation expense	9,979	9,036
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(2,557)	(3,166)
Accounts receivable	187	134
Accounts payable	(340)	(361)
Accrued expenses and other liabilities	7	(778)
Net cash used in operating activities	(42,356)	(52,087)
Cash flows from investing activities:		
Purchases of property and equipment	(214)	(43)
Proceeds from sale of property and equipment	—	4
Net cash used in investing activities	(214)	(39)
Cash flows from financing activities:		
Proceeds from stock options exercised	490	374
Proceeds from public offering, net of underwriters' discounts	79,074	—
Proceeds from at the market offering, net of sales commission	5,799	—
Payment of offering costs	(688)	(182)
Net cash provided by financing activities	84,675	192
Net increase (decrease) in cash, cash equivalents and restricted cash	42,105	(51,934)
Cash, cash equivalents and restricted cash, at beginning of period	99,194	151,128
Cash, cash equivalents and restricted cash, at end of period	$ 141,299	$ 99,194
Supplemental disclosure of non-cash investing and financing activities:		
Deferred offering costs not yet paid	$ 4	$ 70
Property and equipment in accounts payable	$ —	$ 11

See accompanying notes to financial statements.

Aptinyx Inc.
Notes to financial statements

1. Organization

Description of business

Aptinyx Inc. (the "Company" or "Aptinyx") was incorporated in Delaware on June 24, 2015 and maintains its headquarters in Evanston, Illinois.

Aptinyx is a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel, proprietary, synthetic small molecules for the treatment of brain and nervous system disorders. Aptinyx has a platform for discovering proprietary compounds that work through a novel mechanism: modulation of N-methyl-D-aspartate receptors ("NMDAr"), which are vital to normal and effective brain and nervous system functions. This mechanism has applicability across a number of brain and nervous system disorders.

Liquidity and capital resources

The Company has incurred losses and negative cash flows from operations since inception and had an accumulated deficit of $213.0 million as of December 31, 2020. The Company expects to incur substantial operating losses for the next several years and will need to obtain additional financing in order to complete clinical studies and launch and commercialize any product candidates for which it receives regulatory approval. There can be no assurance that such financing will be available or will be at terms acceptable to the Company.

On July 1, 2019, the Company entered into a Sales Agreement with Cowen and Company, LLC ("Cowen") pursuant to which the Company may offer and sell shares of its common stock with an aggregate offering price of up to $50.0 million under an "at the market" offering program (the "ATM Offering"). The Sales Agreement provides that Cowen will be entitled to a sales commission equal to 3.0% of the gross sales price per share of all shares sold under the ATM Offering. No sales from the ATM occurred in 2019. For the year ended December 31, 2020, the Company sold an aggregate of 1,491,482 shares at a weighted-average price of $3.89 per share for net proceeds of $5.7 million after deducting sales commission and other offering expenses.

On January 14, 2020, the Company completed a follow-on public offering of its common stock pursuant to an effective registration statement on Form S-3. The Company sold an aggregate of 11,691,666 shares of common stock, which included the exercise in full of the underwriters' option to purchase additional shares, at a public offering price of $3.00 per share. Net proceeds from the offering were approximately $33.3 million after deducting underwriting discounts and commissions as well as other offering expenses.

On October 26, 2020, the Company completed a follow-on public offering of its common stock pursuant to an effective registration statement on Form S-3. The Company sold an aggregate of 16,100,000 shares of common stock, which included the exercise in full of the underwriters' option to purchase additional shares, at a public offering price of $3.00 per share. Net proceeds from the offering were approximately $45.1 million after deducting underwriting discounts and commissions as well as other offering expenses.

As of December 31, 2020, the Company had cash and cash equivalents of $141.0 million which, when combined with the proceeds received from the Company's "at the market" discussed below (see Note 16), it believes will be sufficient to fund its planned operations for a period of at least twelve months from the date of the issuance of these financial statements.

2. Basis of presentation

The accompanying financial statements are prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP").

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board ("FASB"), or other standard setting bodies and adopted by the Company as of the specified effective date. Unless otherwise discussed, the impact of recently issued standards that are not yet effective will not have a material impact on the Company's financial statements upon adoption. Under the Jumpstart Our Business Startups Act of 2012, as amended ("the JOBS Act"), the Company meets the definition of an emerging growth company, and has elected the extended transition period for complying with new or revised accounting standards, which delays the adoption of these accounting standards until they would apply to private companies.

Recently adopted accounting pronouncements

In May 2014, the FASB issued Accounting Standards Update ("ASU") 2014-09, *Revenue from Contracts with Customers* ("ASC 606"), which amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in ASC Topic 605, *Revenue Recognition*, ("ASC 605"). Through subsequent targeted amendments, the FASB issued additional ASUs that delayed the effective date of ASC 606 and clarified various aspects of the new revenue guidance, including principal versus agent considerations, identifying performance obligations, licensing, and other improvements and practical expedients. The Company adopted this new standard on January 1, 2019 using the modified retrospective transition method. The Company presents revenue from contracts with customers as collaboration revenue in the Company's statements of operations. The Company applied this new standard to all contracts with customers that were not complete as of the adoption date and has determined that no cumulative catch-up adjustment to accumulated deficit was required. See Note 4, "Research collaboration agreement with Allergan" for additional information regarding the Company's single contract that falls within the scope of ASC 606. The Company considered the adoption of ASC 606 compared to what would have been recognized by the Company under the prior revenue standard, ASC 605. The adoption of ASC 606 did not have a material impact on the Company's financial statements as of and for the year ended December 31, 2019.

In June 2018, the FASB issued ASU 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*. This ASU expands the scope of Topic 718, *Compensation—Stock Compensation* to include share-based payments issued to nonemployees for goods or services. Under the new guidance, the existing employee guidance will apply to nonemployee share based transactions (as long as the transaction is not effectively a form of financing), with the exception of specific guidance related to the attribution of compensation cost. The cost of nonemployee awards will continue to be recorded as if the grantor had paid cash for the goods or services. The Company early adopted this new standard on January 1, 2019. The adoption did not have a material impact on the Company's financial statements.

Recently issued accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASC 842"), which requires a lessee to recognize assets and liabilities on the balance sheet for operating leases and changes many key definitions, including the definition of a lease. The new standard includes a short-term lease exception for leases with a term of 12 months or less, as part of which a lessee can make an accounting policy election not to recognize lease assets and lease liabilities. Lessees will continue to differentiate between finance leases (previously referred to as capital leases) and operating leases using classification criteria that are substantially similar to the previous guidance. The new standard will become effective for the Company for annual reporting periods beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. The Company anticipates that the adoption of this standard will have an impact on its balance sheet due to the recognition of right-of-use assets and lease liabilities; however, the Company is currently evaluating the impact that the adoption of ASC 842 will have on its financial statements.

3. Summary of significant accounting policies

Use of estimates

The financial statements are prepared in conformity with GAAP. This process requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and

liabilities as of the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

Risk and uncertainties

The Company's future results of operations involve a number of risks and uncertainties. Factors that could affect the Company's future operating results and cause actual results to vary materially from expectations include, but are not limited to, uncertainty of: future clinical study results, the scope, rate of progress and expense of the Company's ongoing as well as any additional preclinical studies, clinical studies and other research and development activities, clinical study enrollment rate or design, the manufacturing of the Company's product candidates, significant and changing government regulation, and the timing and receipt of any regulatory approvals.

The Company's product candidates require approvals from the U.S. Food and Drug Administration and comparable foreign regulatory agencies prior to commercial sales in their respective jurisdictions. There can be no assurance that any product candidates will receive the necessary approvals. If the Company was denied approval, approval was delayed or the Company was unable to maintain approval for any product candidate, it could have a materially adverse impact on the Company.

The Company is dependent upon third-party manufacturers to supply product 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 final drug product related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and final drug product.

A novel strain of coronavirus (COVID-19) was first identified in December 2019, and subsequently declared a global pandemic by the World Health Organization on March 11, 2020. As a result of the outbreak, many companies have experienced disruptions in their operations and in markets served. On March 27, 2020, the Company suspended patient enrollment for certain ongoing Phase 2 clinical studies, including its NYX-2925 studies in painful diabetic peripheral neuropathy and fibromyalgia and its NYX-483 study in Parkinson's disease cognitive impairment. The Company began re-enrollment in its NYX-2925 study in fibromyalgia in September 2020 and painful diabetic peripheral neuropathy in January 2021. The Company has initiated some and may take additional temporary precautionary measures intended to help ensure the well-being of its employees and minimize business disruption. The Company considered the impact of COVID-19 on the assumptions and estimates used and determined that there were no material adverse impacts on the Company's results of operations and financial position at December 31, 2020. The full extent of the future impacts of COVID-19 on the Company's operations is uncertain. A prolonged outbreak could have a material adverse impact on financial results and business operations of the Company, including the availability of capital, timing and ability of the Company to complete certain clinical studies, and other efforts required to advance the development of its targets.

Revenue recognition

Revenue is recognized in accordance with revenue recognition accounting guidance, which utilizes five steps to determine whether revenue can be recognized and to what extent: (i) identify the contract with a customer; (ii) identify the performance obligation(s); (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) determine the recognition period. The Company only applies the five-step model to contracts when it is probable that the Company will collect the consideration it is entitled to 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, *Revenue from Contracts with Customers,* the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. 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.

Significant judgments exercised by management include the identification of performance obligations, and whether such promised goods or services are considered distinct. The Company evaluates promised goods or services on a contract by contract basis to determine whether each promise represents a good or service that is distinct or has the same pattern of

transfer as other promises. A promised good or service is considered distinct if the customer can benefit from the good or service independently of other goods/services either in the contract or that can be obtained elsewhere, without regard to contract exclusivity, and the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contact. If the good or service is not considered distinct, the Company combines such promises and accounts for them as a single combined performance obligation.

Accounts receivable

Accounts receivable that management has the intent and ability to collect are reported in the balance sheets at outstanding amounts, less an allowance for doubtful accounts. During the years ended December 31, 2020 and 2019, one research collaborator, Allergan plc ("Allergan") represented 100% of the Company's revenues (see Note 4). The associated accounts receivable were approximately $0.3 million and $0.4 million at December 31, 2020 and 2019, respectively. The Company writes off uncollectible receivables based on specific identification when the likelihood of collection is remote. No allowance was deemed necessary at December 31, 2020 and 2019.

Cash, cash equivalents and restricted cash

Cash and cash equivalents consist of cash and, if applicable, highly liquid investments with an original maturity of three months or less when purchased. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the balance sheets that sum to the total of the same such amounts shown in the statements of cash flows (amounts in thousands).

	As of December 31,	
	2020	**2019**
Cash and cash equivalents	$ 141,028	$ 98,849
Short-term and long-term restricted cash	271	345
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$ 141,299	$ 99,194

Amounts included in restricted cash represent those amounts required to be held as a security deposit in the form of letters of credit for the Company's leased office facility and cash collateral held by credit card.

Concentrations of credit risk

The Company, at times, maintains cash and cash equivalents in accounts with a financial institution in excess of the amount insured by the Federal Deposit Insurance Corporation. The Company monitors the financial stability of this institution regularly and management does not believe there is significant credit risk associated with deposits in excess of federally insured amounts.

Fair value of financial instruments

ASC 820, *Fair Value Measurement* ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances.

ASC 820 identifies fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering

market participant assumptions in fair value measurements, ASC 820 establishes a three-tier fair value hierarchy that distinguishes between the following:

- Level 1 inputs are quoted prices (unadjusted) in active markets for identical assets or liabilities;
- Level 2 inputs are inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly; and
- Level 3 inputs are unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability. Financial assets and liabilities are classified in their entirety based on the lowest level of input that is significant to the fair value measurement.

To the extent that the 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. There were no Level 3 assets or liabilities as of December 31, 2020 or 2019.

The carrying values reported in the Company's balance sheets for cash and cash equivalents, restricted cash, accounts receivable, accounts payable, and accrued expenses are reasonable estimates of their fair values due to the short-term nature of these items.

Property and equipment

Property and equipment are stated at cost. Maintenance and repairs are charged to expense as incurred. Additions, improvements and replacements are capitalized. Depreciation of property and equipment is provided for by the straight-line method over the estimated useful lives of the related assets. The estimated useful lives of property and equipment are as follows:

Description	Estimated useful life
Computer software and equipment	3 years
Office equipment and furniture	5 years
Laboratory equipment	5 years
Leasehold improvements	Lesser of the estimated useful life or term of the lease

Construction-in-progress reflects property and equipment yet to be placed in service.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. If the sum of the estimated future undiscounted cash flows expected to result from the use and eventual disposition of an asset is less than the carrying amount of the asset group, an impairment loss is recognized. Measurement of an impairment loss is based on the fair value of the asset group. The Company has not recorded any impairment losses on long-lived assets for the years ended December 31, 2020 and 2019.

Research and development

Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, depreciation, contract services and other related costs. Research and development costs are expensed to operations as the related obligation is incurred.

The Company has entered into various research and development contracts with research institutions, clinical research organizations, clinical manufacturing organizations and other companies. These agreements are generally cancelable, and related payments are recorded as research and development expenses as incurred. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected on the balance sheet as prepaid or accrued expenses. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Stock-based compensation

The Company has stock-based compensation plans that cover the Company's directors and employees and are more fully described in Note 11. Stock-based compensation cost is estimated at the grant date based on the fair value of the award, and the cost is recognized as expense ratably over the vesting period.

Income taxes

The Company accounts for income taxes under the liability method in accordance with FASB ASC 740, *Income Taxes*. Under this method, deferred income tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is established if it is more likely than not that all, or some portion, of deferred income tax assets will not be realized. The Company has recorded a full valuation allowance to reduce its net deferred income tax assets to zero. The valuation allowance increased by $6.9 million and $16.4 million during the years ended December 31, 2020 and 2019, respectively. In the event the Company were to determine that it would be able to realize some or all its deferred income tax assets in the future, an adjustment to the deferred income tax asset valuation allowance would increase income in the period such determination was made.

The Company recognizes the effect of income tax positions only if those positions are more likely than not of being sustained upon an examination. Any recognized income tax positions would be measured at the largest amount that is greater than 50% likely of being realized. Changes in recognition or measurement would be reflected in the period in which the change in judgment occurs. At December 31, 2020 and 2019, the Company had no liability for income tax associated with uncertain tax positions. The Company would recognize any corresponding interest and penalties associated with its income tax positions in income tax expense. There was no income tax interest or penalties incurred in 2020 or 2019.

Segment data

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is on advancing therapies to treat disorders of the brain and nervous system. All tangible assets are held in the United States and all revenue is generated in the United States.

Comprehensive loss

Comprehensive loss is equal to net loss as presented in the accompanying statements of operations.

Net loss per share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is the same as basic net loss per share, since the effects of potentially dilutive securities are antidilutive given the Company has reported net losses for each period presented.

4. Research collaboration agreement with Allergan

On July 24, 2015, the Company entered into a Research Collaboration Agreement ("RCA") with Naurex Inc., a subsidiary of Allergan plc ("Allergan"), which became a wholly owned subsidiary of AbbVie Inc. in May 2020. Under the terms of the agreement, the RCA will terminate upon the earlier of (i) 180 days after a predetermined anniversary of the effective date of the RCA and (ii) the date on which Allergan exercises the last of three options to acquire molecules from a pool of eligible compounds in both cases (clauses (i) and (ii)) subject to potential extension if and as required for the Company to transfer to Allergan information and technology related to compounds that were licensed by Allergan. The jointly funded research activities and option exercise period under the RCA, including the associated payments by Allergan to the Company, came to their contractual conclusion in August 2020 and February 2021, respectively. Under the terms of the agreement, Allergan will pay the Company $1.0 million for each option exercised by Allergan. On May 16, 2018 and February 23, 2021, Allergan exercised its first and second option to acquire exclusive rights to develop and commercialize AGN-241751 and AGN-281705 within a predefined set of indications.

The Company concluded that Allergan meets the definition of a customer, and therefore concluded that the RCA represents a contract with a customer that falls within the scope of ASC 606.

Performance obligations

The Company identified the following promised goods or services within the RCA:

- Research Licenses – the Company provides access to exclusive licenses under all of the Company's NMDAr technologies, during the research term for the sole purpose of conducting research and development activities (the "Research Licenses"). Historically, the Company's licenses have held no value to the customer on a standalone basis, as the research compounds were in the early discovery phase and required the Company's expertise for further development. Accordingly, the Research Licenses are not considered distinct.
- Research and Development Services – the Company provides Research and Development Services that are performed on behalf of, or with, Allergan (the "Research and Development Services"). As discussed within Research Licenses above, the Company's licenses have historically held no value without the specialized research and development services. As the Company generally only provides Research and Development Services for internally generated small molecules that modulate NMDArs which require a license to be utilized by a third party, the Research and Development Services are not considered distinct.
- Joint Steering Committee – the Company actively participates in a joint steering committee, which allows the Company and its collaboration partner to direct the progression and prioritization of the joint discovery programs. As the JSC would not occur or benefit the customer without the use of the Research Licenses and the related Research and Development Services, and given the Company's proprietary knowledge of the Research Licenses and the NMDAr technologies, this is not considered distinct.

The Company also evaluated whether the option granted to the customer to acquire additional goods or services represented a material right at contract inception. Upon Allergan's exercise of one of its options, the Company is obligated to transfer control of all intellectual property relating to the optioned compound to Allergan, after which the Company has no further interest in, or continuing involvement with, such optioned compound. The Company evaluated the customer options for material rights, that is, whether the option was to acquire additional goods or services for free or at a discount, and concluded that the options are priced, at contract inception, at standalone selling price. Consequently, the customer options do not represent a performance obligation at the outset of the arrangement since they are contingent upon the option exercise which is outside of the Company's control.

The Company has concluded that there is a single combined performance obligation (comprising the Research Licenses, Research and Development Services and participation in the JSC) which is satisfied over time, as the Research and Development Services are performed. The exercise of the option to acquire exclusive rights to develop and commercialize AGN-241751 or any future options exercised are not considered a performance obligation until the time of option exercise.

Transaction price

The RCA includes both fixed and variable consideration. Fixed payments, such as contractually defined fees per full-time employee ("FTE"), are included in the transaction price at contract inception, while variable consideration, such as reimbursement for Research and Development Services, are estimated and then evaluated for constraints upon inception of the contract and evaluated on a quarterly basis thereafter. Research and Development Services are updated for actual invoices. There were no capitalized costs associated with obtaining the contract.

The Company uses an input method to measure proportional performance and to calculate the corresponding amount of revenue to recognize. The Company uses fixed FTE efforts and variable out-of-pocket costs as actual costs incurred relative to the annual budget research plan to measure progress towards fulfillment of the performance obligation. An input method of revenue recognition requires management to make estimates of costs to complete the Company's performance obligations. In making such estimates, significant judgment is required to evaluate assumptions related to cost estimates. The cumulative effect of revisions to estimated costs to complete the Company's performance obligations will be recorded in the period in which changes are identified and amounts can be reasonably estimated. The Company does not anticipate significant changes as the research plan is reviewed and adjusted annually and approved by the JSC. There are no significant financing components in the contract.

The Company has determined that the option fee is representative of standalone selling price and concluded that it will recognize revenue for the option fee at a point in time, on the date of exercise, due to the significant uncertainty of whether or not Allergan would exercise the option. The Company recognizes the option fee at a point in time because control of the underlying intellectual property transfers to the customer, and the customer is able to use and benefit from the license. The Company has no further rights, interests or remaining performance obligations associated with any optioned compound, once exercised.

During the years ended December 31, 2020 and 2019, the Company recorded expenses of $3.2 million and $7.3 million, respectively, for certain development activities in accordance with the terms of the RCA, of which 50% was reimbursed by Allergan. The Company received reimbursements of $1.6 million and $3.7 million during the years ended December 31, 2020 and 2019, respectively. Such reimbursements were reported within collaboration revenue in the statements of operations.

5. Fair value measurements

Assets measured at fair value as of December 31, 2020 are as follows (in thousands):

	December 31, 2020	Level 1	Level 2	Level 3
Assets				
Money market funds, included in cash and cash equivalents	$ 140,283	$ 140,283	$ —	$ —
Money market funds, included in restricted cash	179	179	—	—
Money market funds, included in other assets	92	92	—	—
	$ 140,554	$ 140,554	$ —	$ —

Assets measured at fair value as of December 31, 2019 are as follows (in thousands):

	December 31, 2019	Level 1	Level 2	Level 3
Assets				
Money market funds, included in cash and cash equivalents	$ 97,998	$ 97,998	$ —	$ —
Money market funds, included in restricted cash	179	179	—	—
Money market funds, included in other assets	166	166	—	—
	$ 98,343	$ 98,343	$ —	$ —

6. Prepaid expenses and other current assets

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

	As of December 31, 2020	As of December 31, 2019
Prepaid clinical	$ 6,052	$ 3,719
Prepaid insurance	1,177	994
Prepaid manufacturing costs	613	558
Other prepaid expenses and current assets	298	366
Total prepaid expenses and other current assets	$ 8,140	$ 5,637

7. Property and equipment

Property and equipment are as follows (in thousands):

	As of December 31, 2020	As of December 31, 2019
Computer software and equipment	$ 15	$ 15
Office equipment and furniture	176	176
Laboratory equipment	1,801	1,597
Leasehold improvements	1,062	1,051
Construction-in-progress	—	11
Less accumulated depreciation	(2,144)	(1,646)
Property and equipment, net	$ 910	$ 1,204

Depreciation expense was $0.5 million for each of the years ended December 31, 2020 and 2019.

8. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consist of the following (in thousands):

	As of December 31, 2020	As of December 31, 2019
Employee-related expenses	$ 2,039	$ 1,925
Development costs and sponsored research	897	652
Clinical trials	195	410
Other	243	354
Total accrued expenses and other current liabilities	$ 3,374	$ 3,341

9. Operating leases

The Company enters into various non-cancelable, operating lease agreements for its facilities and equipment in order to conduct its operations. The Company expenses rent on a straight-line basis over the life of the lease and has recorded deferred rent on the balance sheets within both accrued expenses and other current liabilities and other long-term liabilities.

On October 13, 2016, the Company entered into a lease agreement with the landlord for office space totaling approximately 16,500 square feet. The term of this lease commenced on April 1, 2017 and continues through August 31, 2022. The Company has an option to renew the lease for one renewal term of 5 years. The lease provided the Company with a tenant improvement allowance of $0.4 million. The Company recorded the tenant improvement allowance incurred as a deferred lease incentive and is amortizing the deferred lease incentive through a reduction of rent expense ratably over the lease term.

On July 18, 2018, the Company entered into a sublease agreement for additional office space adjacent to the Company's existing headquarters in Evanston, Illinois, totaling approximately 6,172 square feet. The term of the lease commenced on July 18, 2018 and continues through September 30, 2022. On January 31, 2019, the sublease agreement was terminated, and the Company entered into an amended lease agreement with the landlord for the same additional office space. The terms commence on February 1, 2019 and continue through August 31, 2022.

Total rent expense, inclusive of lease incentives, under the operating lease agreements amounted to $0.9 million for each of the years ended December 31, 2020 and 2019, respectively.

Aggregate future minimum annual rental commitments under these non-cancelable lease agreements are as follows at December 31, 2020 (in thousands):

Year ending December 31,	
2021	$ 916
2022	617
2023	—
2024	—
2025	—
Thereafter	—
	$ 1,533

10. Stockholders' equity

Preferred Stock

The Company is also authorized to issue 10 million shares of undesignated preferred stock, par value $0.01, in one or more series. As of December 31, 2020, no shares of preferred stock were issued or outstanding.

Common stock

As of December 31, 2020 and 2019, the Company had reserved common stock for issuance as follows (in thousands):

	As of December 31,	
	2020	2019
Stock options issued and outstanding	6,684	4,798
Unvested restricted stock units	1,091	1,032
	7,775	5,830

11. Stock incentive plan

In October 2015, the Company established a stock option plan ("2015 Plan") to provide for the issuance of shares of common stock pursuant to stock options, stock appreciation rights, stock purchase rights, restricted stock agreements and long-term performance awards granted to key employees, directors and consultants of the Company.

On June 5, 2018, the Company's stockholders approved the 2018 Stock Option and Incentive Plan (the "2018 Plan"), which became effective on June 20, 2018. The number of shares available for grant under the Company's 2018 Plan as of December 31, 2020 was 2,243,984 which includes 505,046 shares of the Company's common stock reserved under the Company's 2015 Plan that became available for issuance upon the effectiveness of the 2018 Plan. No future issuance will be made under the 2015 Plan.

The number of shares available for grant under the Company's stock option plan were as follows (in thousands):

Available for grant as of January 1, 2019	3,817
Plan amendment	1,341
Grants	(2,955)
Forfeitures and cancellations	878
Available for grant as of December 31, 2019	3,081
Plan amendment	1,348
Grants	(3,071)
Forfeitures and cancellations	886
Available for grant as of December 31, 2020	2,244

Stock-based compensation expense

Non-cash stock-based compensation expense recognized in the accompanying statements of operations relating to both stock options and restricted stock awards for the years ended December 31, 2020 and 2019 are as follows (in thousands):

	Year ended December 31,	
	2020	2019
Research and development	$ 2,259	$ 2,442
General and administrative	7,720	6,594
Total stock-based compensation expense	$ 9,979	$ 9,036

Restricted stock awards

During the year ended December 31, 2020, the Company issued 6,392 restricted stock awards to a board member that vested immediately on the date of grant. Non-cash restricted stock award expense recognized in the accompanying statements of operations was less than $0.1 million and $0.2 million for the years ended December 31, 2020 and 2019, respectively. The total fair value of shares that vested in 2020 was less than $0.1 million. As of December 31, 2020, there were no unvested restricted stock awards.

Restricted stock units

In June 2020 and May 2019, the Company issued an aggregate of 205,200 and 1,183,400 restricted stock units, respectively, to employees. The restricted stock units issued in 2020 vest ten months from the date of grant. The restricted stock units issued in 2019 vest two years from the date of grant. The Company at any time may accelerate the vesting of the restricted stock units. Such shares are not accounted for as outstanding until they vest.

The table below summarizes activity related to restricted stock units (in thousands, except per share amounts):

	Shares		Weighted-average grant date fair value per share
Unvested as of December 31, 2019	1,032	$	3.63
Issued	205	$	3.61
Vested	(21)		3.63
Forfeited and canceled	(125)		3.63
Unvested as of December 31, 2020	1,091	$	3.63

Non-cash restricted stock unit award expense recognized in the accompanying statements of operations was $2.0 million and $1.3 million for the years ended December 31, 2020 and 2019. At December 31, 2020, there was $0.8 million of unrecognized compensation cost that will be recognized as expense over a weighted-average period of 0.34 years.

Stock options

During the years ended December 31, 2020 and 2019, the Company granted 2.9 million and 1.8 million stock options, respectively. The options have a ten-year life and generally vest over a period of four years, subject to continuous employment.

The weighted-average grant date fair value per share of each option granted during the years ended December 31, 2020 and 2019 was $2.09 and $7.98, respectively. As of December 31, 2020, there was $13.7 million of unrecognized compensation cost related to non-vested stock options which is expected to be recognized over a weighted-average period of 2.19 years.

The fair value of each option award is estimated on the date of grant using a Black-Scholes option pricing valuation model that uses various assumptions regarding the: (1) expected volatility, (2) expected life of the option, (3) expected dividend yield, and (4) risk-free interest rate. The Company uses the historical volatility of the share values of publicly traded companies within the biotech industry as a surrogate for the expected volatility of the Company's common stock. A zero-dividend yield is also assumed in the stock option fair value computations. The expected life of the options represents the period of time that the options granted are expected to be outstanding and has been calculated utilizing the "simplified method" for awards that qualify as "plain vanilla" options. The risk-free rate is based on 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.

The specific assumptions used to determine the fair value of the stock options granted during the years ended December 31, 2020 and 2019 were as follows:

	Year ended December 31,	
	2020	2019
Expected volatility	76%-82%	71%-75%
Expected dividends	None	None
Expected option life	5.00 - 6.08 Years	5.00 - 6.08 Years
Risk-free rate	0.28 – 1.18%	1.38 – 2.72%

The table below summarizes activity related to stock options (in thousands, except per share amounts):

Options	Shares	Weighted-average exercise price	Weighted-average remaining contractual term	Aggregate intrinsic value
Outstanding, January 1, 2019	3,959	$ 7.46	8.79	$ 35,984
Granted	1,772	12.19		
Exercised	(181)	2.07		
Forfeited and canceled	(752)	11.70		
Outstanding, December 31, 2019	4,798	$ 8.75	8.29	$ 1,159
Granted	2,859	3.17		
Exercised	(212)	2.32		
Forfeited and canceled	(761)	5.96		
Outstanding, December 31, 2020	6,684	$ 6.88	7.96	$ 1,582
Vested and expected to vest at December 31, 2020	6,684	$ 6.88	7.96	$ 1,582
Exercisable at December 31, 2020	3,210	$ 7.40	7.07	$ 931

Employee stock purchase plan

On June 5, 2018, the Company's stockholders approved the 2018 Employee Stock Purchase Plan (the "ESPP"), which became effective upon the completion of the Company's initial public offering. A total of 314,697 shares of common stock were initially reserved for issuance under this plan. In addition, the number of shares of common stock that may be issued under the ESPP automatically increase on January 1 of each year through January 1, 2028, by the lesser of (i) 1% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 and (ii) such lesser number of shares as determined by the administrator of the Company's ESPP.

12. Net loss per share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows for the years ended December 31, 2020 and 2019 (in thousands, except per share data):

	Year ended December 31,	
	2020	2019
Numerator:		
Net loss attributable to common stockholders	$ (50,053)	$ (57,410)
Denominator:		
Weighted-average common shares outstanding—basic and diluted	48,866	33,556
Net loss per share attributable to common stockholders—basic and diluted	$ (1.02)	$ (1.71)

The following common stock equivalents outstanding as of December 31, 2020 and 2019, were excluded from the computation of diluted net loss per share attributable to common stockholders for the periods presented because including them would have been anti-dilutive (in thousands):

	As of December 31,	
	2020	2019
Stock options issued and outstanding	6,684	4,798
Unvested restricted stock units	1,091	1,032
	7,775	5,830

13. Employee benefit plan

Effective December 31, 2015, the Company established a defined contribution 401(k) plan (the "401(k) Plan") for the benefit of its employees. All of the employees of the Company are eligible to participate in the 401(k) Plan which permits employees to make voluntary contributions up to the dollar limit allowed under the Internal Revenue Code. The 401(k) Plan also provides for matching contributions as defined by the Company of up to a combined total of 4% of an employee's eligible annual compensation. The Company has recorded matching contributions of $0.3 million and $0.4 million for the years ended December 31, 2020 and 2019, respectively.

14. Income taxes

Provision for income taxes

There is no provision for income taxes because the Company has historically incurred operating losses and maintains a full valuation allowance against its net deferred tax assets. The reported amount of income tax expense for the years differs from the amount that would result from applying domestic federal statutory tax rates and pretax losses primarily because of changes in valuation allowance.

Deferred tax assets and valuation allowance

Deferred tax assets reflect the tax effects of net operating losses ("NOLs") and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The most significant item of deferred tax assets is derived from the Company's federal NOLs. At December 31, 2020, the Company had a U.S. federal NOL carryforward available to offset future taxable income of $186.5 million. This includes $184.8 million of gross NOLs that are limited under Sec. 382 of the Internal Revenue Code, of which $48.9 million gross NOLs were generated prior to 2018 and will begin to expire in 2035, and the remainder were generated after 2018 and have an indefinite carryforward period. All the gross NOLs that are limited are subject to a substantial annual limitation and $33.3 million will expire based on such limitations. There could also be additional ownership changes in the future which may result in additional limitations on the utilization of NOL carryforwards. As of December 31, 2020, the Company had state NOL carryforwards of $17.7 million which have a 12-year carryforward period and will begin to expire starting in 2027.

A reconciliation of the U.S statutory rate to the Company's effective tax rate is as follows:

Year ended December 31,	2020	2019
Federal rate	21.0 %	21.0 %
State rate	7.5	7.5
Valuation allowance	(27.8)	(28.6)
Other	(0.7)	0.1
	— %	— %

The significant components of the Company's net deferred tax assets are as follows (in thousands):

December 31,	2020	2019
Deferred tax assets		
Net operating loss	$ 46,158	$ 41,727
Stock-based compensation	5,053	2,603
Accrued clinical trials	99	176
Accrued compensation	571	509
Accrued expenses and other, net	452	383
Total deferred tax assets	52,333	45,398
Less valuation allowance	$ (52,333)	$ (45,398)
Net deferred tax assets	—	—
Net deferred taxes	$ —	$ —

The Company files federal and state income tax returns and, in the normal course of business, the Company is subject to examination by these taxing authorities. As of December 31, 2020, the Company's tax years through December 31, 2015 are subject to examination by the U.S. federal and state taxing authorities. The December 31, 2018 tax year is currently under examination by the Internal Revenue Service.

15. Commitments and contingencies

From time to time, the Company is subject to occasional lawsuits, investigations and claims arising out of the normal conduct of business. The Company has no significant pending or threatened litigation as of December 31, 2020.

In the normal course of business, the Company enters into contracts that contain a variety of indemnifications with its employees, licensors, suppliers and service providers. Further, the Company indemnifies its directors and officers who are, or were, serving at the Company's request in such capacities. The Company's maximum exposure under these arrangements is unknown at December 31, 2020. The Company does not anticipate recognizing any significant losses relating to these arrangements.

16. Subsequent events

ATM Offering

On January 20, 2021, the Company sold under the ATM offering an aggregate of 3,629,458 shares at a weighted-average price of $4.03 per share for net proceeds of $14.5 million after deducting sales commission and other offering expenses.

Allergan exercise of AGN-281705

On February 23, 2021**,** Allergan exercised its option to acquire exclusive rights to develop and commercialize AGN-281705 within a predefined set of indications in exchange for $1.0 million.

Item 16. Form 10-K Summary

The Company has elected not to include summary information.

EXHIBIT INDEX

Exhibit No.	Exhibit Index
3.1	Amended and Restated Certificate of Incorporation of the Registrant, incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-38535 filed with the SEC on June 25, 2018).
3.2	Amended and Restated Bylaws of the Registrant, incorporated by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K (File No. 001-38535 filed with the SEC on June 25, 2018).
4.1	Specimen stock certificate evidencing the shares of common stock incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on June 11, 2018).
4.2	Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, dated December 11, 2017, incorporated by reference to the Registrant's Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on May 23, 2018).
4.3	Description of Registrant's Securities
10.1#	2015 Stock Option and Grant Plan, amendments thereto, and forms of award agreements thereunder, incorporated by reference to the Registrant's Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on May 23, 2018).
10.2#	2018 Stock Option and Incentive Plan and forms of award agreements thereunder, incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on June 11, 2018).
10.3#	2018 Employee Stock Purchase Plan, incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on June 11, 2018).
10.4#	2018 Senior Executive Cash Bonus Plan, incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1(File No. 333-225150 filed with the SEC on June 11, 2018).
10.5*	Non-Employee Director Compensation Policy.
10.6#	Form of Indemnification Agreement, incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on June 11, 2018).
10.7†	Research Collaboration Agreement by and between Naurex Inc. (a wholly-owned subsidiary of Allergan plc) and the Registrant, dated as of July 24, 2015, as amended by Amendment No. 1, dated July 15, 2016, incorporated by reference to the Registrant's Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on May 23, 2018).
10.8#	Form of Amended and Restated Employment Agreement, incorporated by reference to the Registrant's First Amendment to the Registration Statement on Form S-1 (File No. 333-225150 filed with the SEC on June 11, 2018).
10.9	Office Lease Agreement by and between FSP 909 Davis Street LLC and Registrant, dated as of October 13, 2016, incorporated by reference to the Registrant's Registration Statement on Form S-1 (File No. 333-225150 filed on May 23, 2018).
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Deloitte & Touche LLP, Independent Registered Public Accounting Firm
31.1*	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Chief Financial Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1**	Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by Norbert Riedel, Chief Executive Officer of the Company, and Ashish Khanna, Chief Financial Officer of the Company.

101	The following materials from Aptinyx Inc.'s Annual Report on Form 10-K for the year ended December 31, 2020, formatted in XBRL (Extensible Business Reporting Language): (i) the Balance Sheets, (ii) the Statements of Operations and Comprehensive Loss, (iii) the Statements of Convertible Preferred Stock and Stockholders' Equity, (iv) the Statements of Cash Flows and (iv) Notes to Financial Statements.

† Confidential treatment has been granted for portions of this Exhibit pursuant to Rule 406 promulgated under the Securities Act of 1933, as amended.

* Filed herewith.

# Indicates a management contract or any compensatory plan, contract or arrangement.

** The certifications furnished in Exhibit 32.1 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

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.

APTINYX INC.

By: /s/ NORBERT G. RIEDEL
Norbert G. Riedel, Ph.D.
Chief Executive 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.

Name	Title	Date
/s/ NORBERT G. RIEDEL Norbert G. Riedel, Ph.D.	Director and Chief Executive Officer (Principal Executive Officer)	March 24, 2021
/s/ ASHISH KHANNA Ashish Khanna	Chief Financial Officer and Chief Business Officer (Principal Financial Officer and Principal Accounting Officer)	March 24, 2021
/s/ PATRICK G. ENRIGHT Patrick G. Enright	Chairman of the Board of Directors	March 24, 2021
/s/ HENRY GOSEBRUCH Henry O. Gosebruch	Director	March 24, 2021
/s/ ELISHA P. GOULD III Elisha P. Gould III	Director	March 24, 2021
/s/ ROBERT J. HOMBACH Robert J. Hombach	Director	March 24, 2021
/s/ ADAM M. KOPPEL Adam M. Koppel, M.D., Ph.D.	Director	March 24, 2021
/s/ RACHEL E. SHERMAN Rachel E. Sherman	Director	March 24, 2021

Exhibit 4.3

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

The following description of our common stock and preferred stock summarizes the material terms and provisions of our common stock and preferred stock. The following description of our capital stock does not purport to be complete and is subject to, and qualified in its entirety by, our certificate of incorporation and bylaws, which are filed as exhibits to the Annual Report on Form 10-K, and by applicable law. The terms of our common stock and preferred stock may also be affected by Delaware law.

Authorized Capital Stock

Our authorized capital stock consists of 150,000,000 shares of common stock, par value $0.01 per share, and 10,000,000 shares of preferred stock, par value $0.01 per share, all of which shares of preferred stock are undesignated.

Common Stock

The holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of our common stock do not have any cumulative voting rights. Holders of our common stock are entitled to receive ratably any dividends declared by our board of directors out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding preferred stock. Our common stock has no preemptive rights, conversion rights, or other subscription rights or redemption or sinking fund provisions.

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding preferred stock. All outstanding shares are fully paid and non-assessable.

The shares of common stock that we have issued are fully paid and non-assessable and will not have, or be subject to, any preemptive or similar rights.

Undesignated Preferred Stock

Our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon our liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our company or other corporate action. The purpose of authorizing our board of directors to issue preferred stock in one or more series and determine the number of shares in the series and its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. When we issue shares of preferred stock, the shares will fully be paid and non-assessable and will not be subject to any preemptive or similar rights.

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

Our certificate of incorporation and bylaws include a number of provisions that may have the effect of delaying, deferring or preventing another party from acquiring control of us and encouraging persons considering unsolicited

tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board Composition and Filling Vacancies

Our certificate of incorporation provides for the division of our board of directors into three classes serving staggered three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of two-thirds or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office, even if less than a quorum. The classification of directors, together with the limitations on removal of directors and treatment of vacancies, has the effect of making it more difficult for stockholders to change the composition of our board of directors.

No Written Consent of Stockholders

Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our bylaws or removal of directors by our stockholders without holding a meeting of stockholders.

Meetings of Stockholders

Our certificate of incorporation and bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements

Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. Our bylaws specify the requirements as to form and content of all stockholders' notices. These requirements may preclude stockholders from bringing matters before the stockholders at an annual or special meeting.

Amendment to Certificate of Incorporation and Bylaws

Any amendment of our certificate of incorporation must first be approved by a majority of our board of directors, and if required by law or our certificate of incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, board composition, limitation of liability and the amendment of our bylaws and certificate of incorporation must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class. Our bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the bylaws; and may also be amended by the affirmative vote of at least two-thirds of the outstanding shares entitled to vote on the amendment, or, if our board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

Undesignated Preferred Stock

Our certificate of incorporation provides for 10,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of Forum

Our amended and restated bylaws provides 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 (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of or based on a breach of a fiduciary duty owed by any of our current or former directors, officers and employees to us or our stockholders, (iii) any action asserting a claim against us or any of our current or former directors, officers, employees or stockholders arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws, or (iv) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein. Our amended and restated bylaws further provide that, unless we consent in writing to an alternative forum, the United States District Court for the Northern District of Illinois will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. In addition, our amended and restated 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 foregoing provisions. We have chosen the United States District Court for the Northern District of Illinois as the exclusive forum for such causes of action because our principal executive offices are located in Evanston, Illinois.

The forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to obtain a favorable judicial forum for disputes with us. The United States District Court for the Northern District of Illinois 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. Although we believe this provision benefits us by providing increased consistency in the application of Delaware law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers.

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our board of directors approved either the business combination or the transaction, which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or

- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

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

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

Nasdaq Global Select Market Listing

Our common stock is listed on The Nasdaq Global Select Market under the trading symbol "APTX."

Exhibit 10.5

APTINYX INC.

NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

The purpose of this **NON-EMPLOYEE DIRECTOR COMPENSATION POLICY** of Aptinyx Inc. (the "**Company**"), is to provide a total compensation package that enables the Company to attract and retain, on a long- term basis, high-caliber directors who are not employees or officers of the Company or its subsidiaries. In furtherance of the purpose stated above, all non-employee directors shall be paid compensation for services provided to the Company as set forth below:

Cash Retainers

Annual Retainer for Board Membership: $35,000 for general availability and participation in meetings and conference calls of our Board of Directors, to be paid quarterly in arrears, pro-rated based on the number of actual days served by the director during such calendar quarter.

Additional Annual Retainer for Non-Executive Chair of the Board:	$	30,000
Additional Retainers for Committee Membership:		
Audit Committee Chair:	$	15,000
Audit Committee member:	$	7,500
Compensation and Management Development Committee Chair:	$	10,000
Compensation and Management Development Committee member:	$	5,000
Nominating and Corporate Governance Committee Chair:	$	8,000
Nominating and Corporate Governance Committee member:	$	4,000

Note: Chair and committee member retainers are in addition to retainers for members of the Board of Directors.

Equity Retainers

Initial Award: An initial, one-time equity award (the "**Initial Award**") of a stock option to purchase 80,000 shares shall be granted to

each new non-employee director upon his or her election to the Board of Directors, which stock option shall vest over a three-year period with one-third of the option shares vesting on the first anniversary of the date of grant and the remaining two-thirds vesting in ratable monthly installments thereafter; *provided*, *however*, that all vesting shall cease if the director resigns from the Board of Directors or otherwise ceases to serve as a director of the Company. Such stock option shall have a per share exercise price equal to the Fair Market Value (as defined in the Company's 2018 Stock Option and Incentive Plan) of the Company's common stock on the date of grant expire ten years from the date of grant.

Annual Award: On each date of the Company's Annual Meeting of Stockholders (the "**Annual Meeting**"), each continuing non-employee member of the Board, other than a director receiving an Initial Award, will receive an annual equity award (the "**Annual Award**") in the form of a stock option to purchase 40,000 shares of the Company's common stock, which shall vest in ratable monthly installments over one year from the date of grant; *provided*, *however*, that all vesting shall cease if the director resigns from the Board of Directors or otherwise ceases to serve as a director, unless the Board of Directors determines that the circumstances warrant continuation of vesting. Such stock option shall have a per share exercise price equal to the Fair Market Value (as defined in the Company's 2018 Stock Option and Incentive Plan) of the Company's common stock on the date of grant and expire ten years from the date of grant.

Expenses: The Company will reimburse all reasonable out-of-pocket expenses incurred by non-employee directors in attending meetings of the Board or any Committee.

Adopted May 28, 2018, subject to effectiveness of the Company's Registration Statement on Form S-1, and as amended on May 15, 2019 and August 26, 2020.

Exhibit 21.1

Subsidiaries of Aptinyx Inc.

None

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statement No. 333-232488 on Form S-3 and Registration Statement Nos. 333-225801 and 333-237508 on Form S-8 of our report dated March 24, 2021, relating to the financial statements of Aptinyx Inc., appearing in this Annual Report on Form 10-K for the year ended December 31, 2020.

/s/ Deloitte & Touche LLP

Chicago, Illinois
March 24, 2021

EXHIBIT 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO RULE 13a-14(a) / 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Norbert G. Riedel, certify that:

1. I have reviewed this Annual Report on Form 10-K of Aptinyx Inc.;

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

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

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

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

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: March 24, 2021

By: /s/ Norbert G. Riedel

Norbert G. Riedel
Chief Executive Officer
(Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO RULE 13a-14(a) / 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Ashish Khanna, certify that:

1. I have reviewed this Annual Report on Form 10-K of Aptinyx Inc.;

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

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

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

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

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: March 24, 2021

By: /s/ Ashish Khanna
Ashish Khanna
Chief Financial Officer and Chief Business Officer
(Principal Financial and Accounting Officer)

EXHIBIT 32.1*

CERTIFICATIONS OF PRINCIPAL EXECUTIVE OFFICER AND PRINCIPAL FINANCIAL OFFICER PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Aptinyx Inc. (the "Company") for the fiscal year ended December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of their knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

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

/s/ Norbert G. Riedel

Norbert G. Riedel
Chief Executive Officer
(Principal Executive Officer)

Dated: March 24, 2021

/s/ Ashish Khanna

Ashish Khanna
Chief Financial Officer and Chief Business Officer
(Principal Financial and Accounting Officer)

Dated: March 24, 2021

* This certification shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, or otherwise subject to the liability of that section, nor shall it be deemed to be incorporated by reference into any filing under the Securities Act of 1933 or the Securities Exchange Act of 1934.