



Aptinyx Inc.

2018 ANNUAL REPORT  
FORM 10-K

**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, 2018  
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. 001-38359

**APTINYX INC.**

(Exact name of registrant as specified in its charter)

Delaware  
(State or other jurisdiction of  
incorporation or organization)

45-4626057  
(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	Name of each exchange on which registered
Common Stock, par value \$0.01 per share	Nasdaq Global Select Market

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

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

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 232.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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 is a shell company (as defined in Rule 12b-2 of the Exchange Act.):  Yes  No

As of June 29, 2018, 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 \$368.2 million based upon the closing sale price of our common stock of \$24.17 on that date.

As of March 18, 2019, there were 33,562,211 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 2019 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, 2018. 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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## 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,” “project,” “should,” “target,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Our business and forward-looking statements involve substantial known and unknown risk and uncertainties, including the risks and uncertainties inherent in our statements regarding:

- the timing, progress, and results of preclinical studies and clinical trials for NYX-2925, NYX-783, NYX-458, and any future product candidates we may develop, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the studies will become available, and our research and development programs;
- the existence or absence of side effects or other properties relating to our product candidates which could delay or prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences following any potential marketing approval;
- the potential for our identified research priorities to advance our technologies;
- the potential benefits of, and our ability to maintain our collaboration with, Allergan plc, or Allergan, and establish or maintain future collaborations or strategic relationships or obtain additional funding in connection with these relationships;
- the potential timelines for our clinical studies or our ability to demonstrate safety and efficacy of our product candidates to the satisfaction of applicable regulatory authorities;
- our ability to obtain and maintain regulatory approval of our product candidates, NYX-2925, NYX-783, NYX-458, and any other future product candidates, and any statements regarding the label of an approved product candidate, including any restrictions, limitations and/or warnings therein;
- our intellectual property position, including the scope of protection we are able to establish and maintain for intellectual property rights covering NYX-2925, NYX-783, NYX-458, and any additional product candidates we may develop, and any statements as to whether we do or do not infringe, misappropriate, or otherwise violate any third-party intellectual property rights;
- our ability and the potential to successfully manufacture our product candidates for clinical studies and for commercial use, if approved;
- our ability to commercialize our products in light of the intellectual property rights of others;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- our plans to research, develop, and commercialize our product candidates;

- our ability to attract collaborators with development, regulatory, and commercialization expertise;
- the size and growth potential of the markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance and clinical utility of NYX-2925, NYX-783, NYX-458, and any future product candidates we may develop, if approved;
- the pricing and reimbursement of NYX-2925, NYX-783, NYX-458, and any future product candidates we may develop, if approved;
- regulatory developments in the United States and foreign countries;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- the success of competing therapies that are or may become available;
- our ability to retain the continued service of our key professionals and to identify, hire, and retain additional qualified professionals;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements, and needs for additional financing;
- our financial performance;
- the impact of laws and regulations, including, without limitation, recently enacted tax reform legislation;
- our expectations regarding the time during which we will be an “emerging growth company” under the Jumpstart Our Business Startups Act;
- our use of proceeds from the initial public offering; and
- other risks and uncertainties, including those listed under “Risk Factors” appearing elsewhere in this Annual Report on Form 10-K.

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. We recently completed a 300-subject study evaluating the safety and efficacy of NYX-2925 in patients with painful diabetic peripheral neuropathy, or painful DPN. We announced in January 2019 that, in the painful DPN study, statistically significant separation from placebo was not observed on the primary endpoint, change in average daily pain from baseline to week four in the total study population. However, the detailed results from the study provide critical findings that inform and support the development path forward for NYX-2925 in chronic pain. We plan to present further detail from this study at the American Pain Society Scientific Meeting in April 2019. We also expect to complete an ongoing exploratory neuroimaging study in patients with fibromyalgia and report data from it in the first half of 2019. NYX-783 is in Phase 2 clinical development for the treatment of post-traumatic stress disorder, or PTSD. We recently initiated a Phase 2a study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of NYX-783 in approximately 144 patients with PTSD – we expect to report data from this study in the first half of 2020. We are currently evaluating the safety, tolerability, and pharmacokinetics of NYX-458 in a Phase 1 study in healthy volunteers, which we expect to complete in the first half of 2019. We intend to develop NYX-458 for the treatment of cognitive impairment associated with Parkinson’s disease.

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 plagued 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 to discover, develop, and commercialize 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 pain conditions.** We believe NYX 2925, if approved, could be a high potential therapy for chronic pain with mechanistic innovations that address significant unmet medical needs. We plan to present detailed findings from the Phase 2 DPN study at the American Pain Society Scientific Meeting in April 2019 and we expect to complete the exploratory fibromyalgia study and report data from the study in the first half of 2019. Together, data from these first-in-patient studies inform and support the future development of NYX 2925 for the treatment of chronic pain.
- **Advance the development of NYX-783 as a novel treatment for PTSD.** We are currently evaluating NYX-783 as a potential treatment for people with PTSD. We recently initiated a Phase 2a study to evaluate the safety and efficacy of NYX-783 in patients with PTSD and expect to report data from this study in the first half of 2020. We believe NYX-783, if approved, could represent a transformative therapeutic option in PTSD that targets the underlying learning and memory dysfunction associated with an inability to extinguish fear caused by trauma, while also addressing the core symptoms and major comorbidities of the disorder.
- **Advance the development of NYX-458 as a novel treatment for Parkinson's disease cognitive impairment.** We are currently evaluating the safety and tolerability of NYX-458 in a Phase 1 clinical study that we expect to complete and report data from in the first half of 2019. Based on compelling data in a highly relevant, translatable, non-human primate model, we believe NYX-458, if approved, may offer substantial improvements over existing treatments for Parkinson's disease cognitive impairment. Our initial Phase 2 study will focus on Parkinson's disease mild cognitive impairment, or PD-MCI.
- **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 our pipeline and other product candidates generated from our discovery platform:

	Indication	Phase 1	Phase 2	Phase 3	Est. U.S. Prevalence	Next Milestone
NYX-2925	Painful Diabetic Peripheral Neuropathy	▶			~5.5mm	Detailed Phase 2a data April 2019
	Fibromyalgia	▶			~5mm	Phase 2a data expected 1H 2019
NYX-783	Post-Traumatic Stress Disorder	▶			~8.5mm	Phase 2a data expected 1H 2020
NYX-458	Parkinson's Disease Cognitive Impairment	▶			~500k	Phase 1 data expected 1H 2019
<b>Additional Program from Our Discovery Platform</b>						
	Indication	Partner	Details			
AGN-241751	Major Depressive Disorder		Acquired by Allergan via exercise of option under ongoing research collaboration. No further economic consideration to Aptinyx associated with future development.			

While all of our product candidates and the other molecules from our discovery platform modulate NMDARs, they are each 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

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 chronic pain as it is established that, when pain becomes chronic (especially neuropathic pain), it becomes increasingly centrally (brain) mediated. 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

We estimate that up to 100 million adults in the United States suffer from chronic pain. While we believe NYX-2925 has the potential to address many chronic pain conditions, we estimate that the initial pain conditions we are targeting affect over 10 million people in the United States – approximately 5.5 million with painful DPN and more than 5 million with fibromyalgia.



## *Phase 2 clinical studies*

Recently we announced that, in our Phase 2 study of NYX 2925 in patients with painful DPN, NYX-2925 demonstrated a very favorable safety profile with no serious adverse events reported. NYX-2925 did not show statistically significant separation from placebo on the primary endpoint of the study. However, signals of analgesic activity were observed and, in a very mechanistically relevant and large sub-group of patients with advanced DPN, NYX-2925 resulted in clinically meaningful and statistically significant improvements in pain and other symptoms. 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 most appropriate dose, patient population, and design to evaluate in future studies. We expect to present further detail from the study at the American Pain Society Scientific Meeting in April 2019. NYX-2925 is also currently being evaluated in a Phase 2 exploratory neuroimaging study in fibromyalgia. In an interim analysis of this study, NYX 2925 was shown to have significant effects on known pain processing markers in the brain, as measured through fMRI. NYX-2925 also exhibited correlated trends towards improvement on the patient-reported outcomes that are being assessed as secondary measures in this study. We expect to complete the exploratory study and report data from it in the first half of 2019. Based on the data from the interim analysis, we expect to initiate a Phase 2 study in fibromyalgia in the second half of 2019.

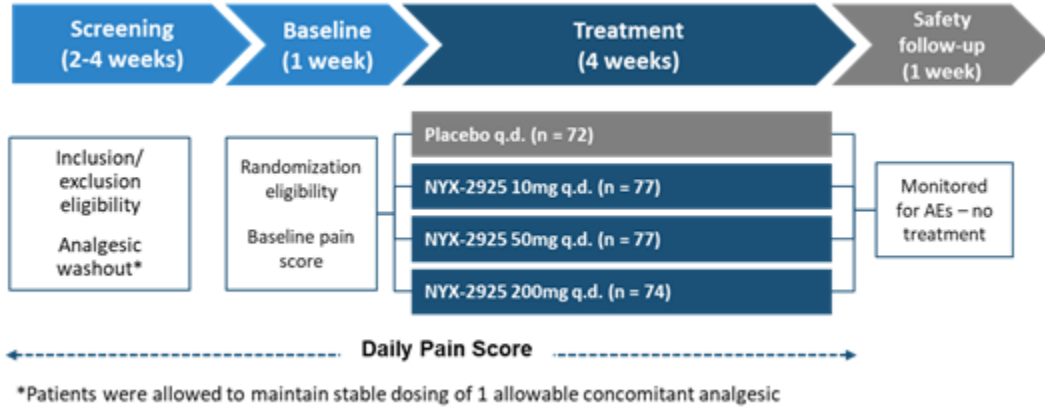
### *Painful diabetic peripheral neuropathy*

We recently completed our Phase 2 clinical study evaluating the safety and efficacy of NYX 2925 in patients with painful DPN. This was a double blind, randomized, placebo-controlled study in 300 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 10mg, 50mg, and 200mg. 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.

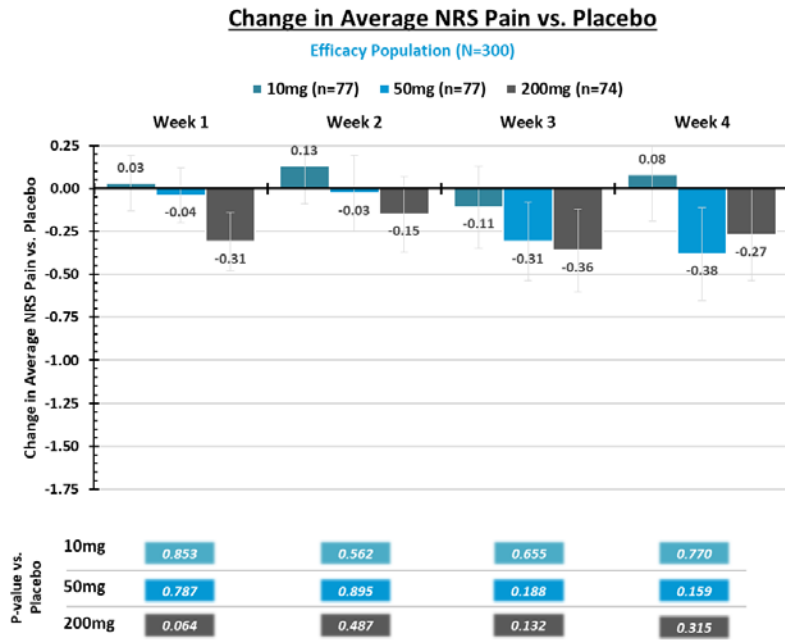
To mitigate high placebo response rates like those seen in similar chronic pain studies, we used an algorithm based on baseline (pre-treatment) pain score reporting as part of the screening process for the study. Patients that exhibited pain reporting characteristics that have been correlated with higher standard deviation and placebo response in historical studies were excluded from the study prior to treatment. This proprietary, masked algorithm was intended to reduce the

variability observed in the study data and to help ensure a robust comparison of pain scores during and after treatment. The figure below illustrates the design of our Phase 2 study in patients with painful DPN.



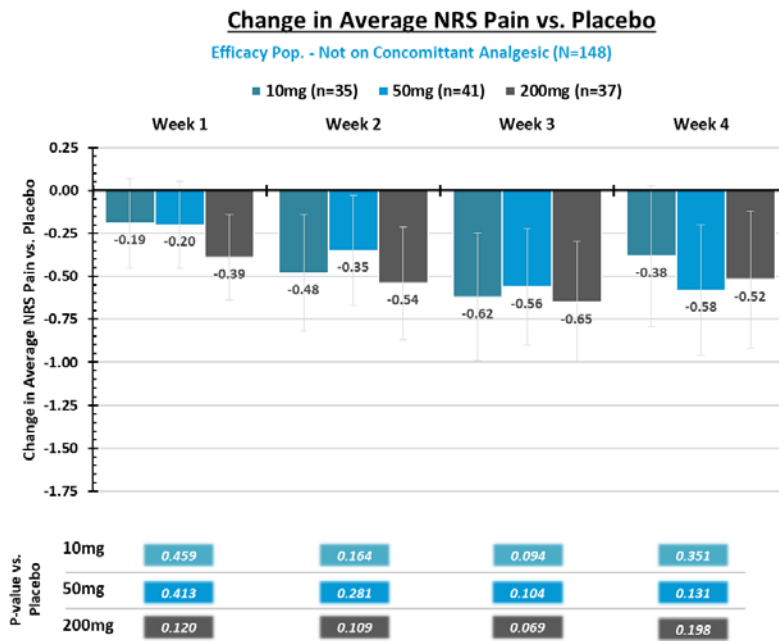
**Results**

We recently reported top-line results from the study, NYX 2925 did not demonstrate statistically significant separation from placebo on the primary endpoint, change in patients’ average daily pain scores on the numeric rating scale, or NRS, during the final treatment week compared to baseline. NYX 2925 exhibited a very favorable safety 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 reached maximal effect by week four, suggesting that a longer treatment period may result in continued improvement and larger drug effect. The graph below summarizes the top-line results in the total efficacy population (N=300) on the primary endpoint compared to placebo.



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

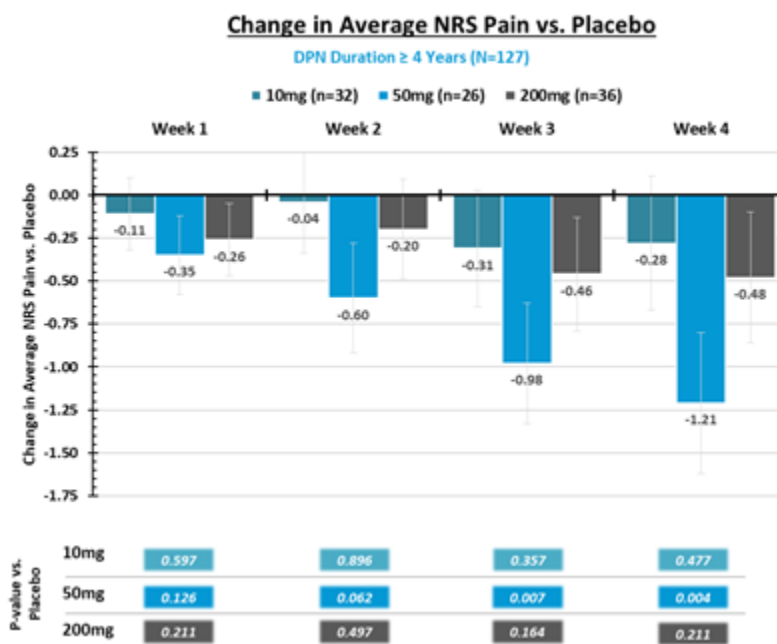
In the total efficacy population, those patients not taking a concomitant analgesic medication (N=148) showed a greater separation on average daily pain scores from placebo. The graph below shows the change in average pain compared to placebo in only those patients who were not taking a concomitant analgesic medication.



*Note: All changes reflect difference in least squares mean change vs placebo 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 very mechanistically relevant sub-group of patients in which NYX-2925 demonstrated a much greater treatment benefit. In this post-hoc 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. 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 below depicts the placebo-adjusted change in average daily pain in the advanced DPN patient sub-group.



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

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

Additionally, and consistent with the findings in the total study population, in advanced DPN patients who were not taking a concomitant analgesic medication, the observed effects of NYX-2925 were even more pronounced. In the 50 mg dose group, the separation from placebo improved to 1.85 points on the NRS at week 4 of treatment.

Based on the safety and efficacy profile exhibited in the study, we believe NYX-2925 has significant potential to address major unmet needs in the treatment of chronic pain. Given the pronounced effects observed in the advanced DPN patient population in this study, we plan to initiate an additional study in painful DPN in the second half of 2019. We expect to present incremental detail on the results from the study at the American Pain Society Scientific Meeting in April 2019.

### Fibromyalgia

We are currently conducting an exploratory neuroimaging study in patients with fibromyalgia. The study is a single-blind, placebo-controlled study. We intend to enroll approximately 24 patients across two U.S.-based academic sites evaluating daily doses of 20 mg and 200 mg.

The goal of the study is 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 are also evaluating additional endpoints, including daily pain scores, and a range of other physical and psychological parameters. Each subject serves as his or her own control, receiving both placebo and NYX-2925 over the course of the six-week study.

We reported positive results from an interim analysis of this exploratory fibromyalgia study in December 2018. We expect to complete the study and report data in the first half of 2019. Based on the results from the interim analysis, we expect to initiate a larger Phase 2 study in patients with fibromyalgia in the second half of 2019.

### *Results of interim analysis*

In the interim analysis conducted in December of 2018, NYX-2925 was shown to significantly reduce pain-evoked glutamate release in the insular cortex, reduce connectivity between the insular cortex and default mode network, 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 suggest that NYX-2925 has an antinociceptive profile. In addition to the positive results shown on the primary imaging endpoints, NYX-2925 also showed favorable corresponding trends on the secondary, patient reported, measures including daily pain scores, fibromyalgia impact questionnaire, and cognition. The interim analysis results provide support to advance NYX-2925 in development for the treatment of fibromyalgia. This study is ongoing, and we expect to complete the study and report data from it in the first half of 2019.

### *Future development*

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

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

### **NYX-783**

NYX-783 is a novel, oral, small-molecule NMDAr modulator in development for the treatment of post-traumatic stress disorder, or PTSD. In a Phase 1 study, 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. We recently initiated a Phase 2a study to evaluate the safety and efficacy of NYX-783 in patients with PTSD and expect to report data from this study in the first half of 2020. Preclinical data suggest that NYX-783 may accelerate fear extinction and inhibit spontaneous fear, potentially addressing a key underlying learning and memory dysfunction associated with PTSD. 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.

### *Phase 2a clinical study*

We recently initiated a first-in-patient Phase 2a study to evaluate the safety, efficacy, and pharmacokinetics of NYX-783 in patients with PTSD. The overarching objective of this study is to inform future studies of NYX-783 on the most appropriate dosing regimen, enrollment criteria, and endpoints to best assess the overall impact of NYX-783 on PTSD symptoms. The study is a randomized, double-blind, placebo-controlled study that will enroll approximately 144 patients. After confirming eligibility and PTSD diagnosis, patients will be randomly assigned to receive placebo or 50 mg of NYX-783 over the course of the eight-week study. The primary efficacy endpoint of the study is the improvement from baseline on the sub scores and total score of the Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, or the CAPS-5. Alongside the primary endpoint, numerous

secondary and exploratory endpoints, exploratory biomarkers, and pharmacodynamic measures are being evaluated in the study. The study is being conducted in two stages, each lasting four weeks. In the first stage, patients will be randomized to placebo or 50 mg of NYX-783 with an overweighting to placebo. At the completion of the first stage, placebo responders and non-responders will be identified in a blinded fashion and each group will then be re-randomized to placebo or 50 mg of NYX-783. Patients that received NYX-783 in the first stage will receive placebo in the second stage. The primary analysis for efficacy in this study will include the groups on NYX-783 and placebo in the first stage and the placebo non-responder group on both NYX-783 and placebo from the second stage. We will also be able to evaluate the durability of effect of NYX-783 through the patients that receive placebo in the second stage after receiving NYX-783 in the first stage.

This study is designed as a proof-of-concept study aimed to characterize the safety and efficacy of NYX-783 and to inform future development for the treatment of PTSD. The various elements of its design are expected to provide a comprehensive understanding of the effects of NYX-783 in the treatment of PTSD.

### ***Future development***

We intend to advance NYX-783 towards regulatory approval for the treatment of PTSD. In addition, we may pursue other neuropsychiatric indications for NYX-783.

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

### **NYX-458**

NYX-458 is a novel, oral, small-molecule NMDAr modulator in development for the treatment of Parkinson's disease cognitive impairment. We are currently evaluating the safety, tolerability, and pharmacokinetics of NYX-458 in a Phase 1 clinical study in healthy volunteers, which we expect to complete and report data from in the first half of 2019. Mechanistic rationale and compelling preclinical data in numerous models of cognitive impairment suggest NYX-458 may be optimally suited to treat cognitive deficits associated with Parkinson's disease.

### ***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 that there are more than 500,000 people in the United States with either PD-MCI or PDD.

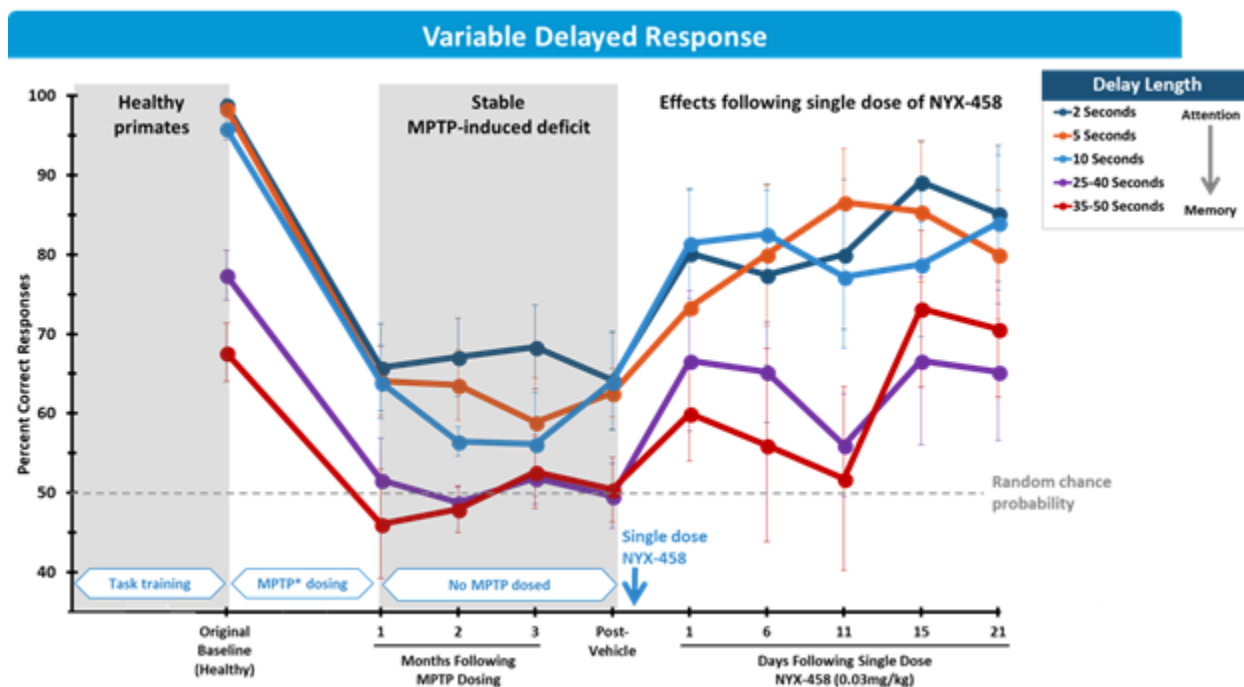
### ***Ongoing Phase 1 clinical study***

We are conducting a Phase 1 study, which we expect to complete in the first half of 2019. This is a randomized, double-blind, sponsor-open, placebo-controlled, single- and multiple-ascending dose, parallel safety, tolerability and pharmacokinetics study of NYX-458 dosed orally in healthy volunteers.

### ***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 highly relevant and translatable, as it evaluates the product candidate's effects in non-human primates by employing the

neurotoxin MPTP to deplete dopamine-related neural 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 baseline levels. The graph below depicts the effect observed in one assay from this model following a single administration of NYX-458.



\*MPTP is a neurotoxin used to deplete dopamine-related neuronal cells – similar to the way Parkinson’s disease does in humans.

### Future development

We intend to develop NYX-458 for the treatment of Parkinson’s disease cognitive impairment.

We are planning our Phase 2 safety and efficacy programs for NYX-458 within Parkinson’s disease and are also considering other causes of cognitive impairment. We believe the mechanism of NYX-458 may be effective across cognitive impairment due to varying etiologies. Based on the results seen in the initial studies in the model of Parkinson’s disease cognitive impairment, we may seek to expand clinical development to other diseases associated with cognitive impairment.

### AGN-241751

Through our research collaboration, Allergan has advanced one compound from our discovery platform into Phase 2 clinical development for the treatment of major depressive disorder. In May 2018, Allergan exercised its option under our collaboration to acquire the exclusive intellectual property rights specific to such compound, triggering payment of a \$1.0 million option fee in connection with such exercise. We will receive no further economic consideration from this product candidate. For more information, see “Research collaboration agreement with Allergan” below.

## 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.

### *NMDA-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 NMDA-targeted therapies, including but not limited to, Adamas Pharmaceuticals Inc., Allergan plc, AmKor Pharma, Inc., Avanir Pharmaceuticals, Inc., Axxome Therapeutics, Inc., Biohaven Pharmaceutical Holding Co. Ltd., Cadent Therapeutics, Inc., Cerecor Inc., Eli Lilly and Company, Genentech Inc., Immune Pharmaceuticals 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., 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, 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 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, ViroMed Inc., and Xenoport 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.



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. There are no therapies currently approved for Parkinson’s mild cognitive impairment in the United States. We are also aware of other companies developing therapies for Parkinson’s disease cognitive impairment, including but not limited to, Anavex Life Sciences, Eli Lilly and Company, and Eisai Pharmaceuticals Inc.

## **Research collaboration agreement with Allergan**

### ***Overview***

In July 2015, we entered into the Allergan Research Collaboration Agreement, 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 reimburses 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 pays us a fixed annual rate per full time employee, or FTE, for each individual assigned to these discovery efforts. Our research activities are supervised by a Joint Steering Committee, or JSC, comprising representatives from both our company and Allergan.

Under the Allergan Research Collaboration Agreement, we are required to use commercially reasonable efforts to perform research activities in accordance with the research collaboration. We propose target compound profiles for use in identifying, discovering, and developing collaboration compounds most suitable for further research and development under the collaboration. Molecules from our discovery platform that meet our mutually agreed upon criteria are designated as “eligible compounds.” When the pool of eligible compounds reaches a certain size, Allergan and we may select, in alternating fashion, molecules from this pool for further investigation.

Allergan may perform research and development on (but not commercialize) molecules it selects as therapies for Alzheimer’s disease, delirium and a list of psychiatric disorders (which list does not include PTSD or substance abuse). 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. Allergan may also exercise up to two more options to acquire commercialization rights to molecules that it previously selected from the pool of eligible compounds. Under this agreement, each time Allergan exercises its option, it is required to pay us an option exercise fee of \$1.0 million and we must (a) assign to Allergan rights in intellectual property that pertains only to the Allergan-optioned compound, and (b) grant Allergan a fully-paid, perpetual, exclusive 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.

We may research and develop molecules we select from the pool of eligible compounds as therapies for any indication outside of Allergan’s field of specified indications. We anticipate we will invent, and therefore own, most intellectual property pertaining to our selected compounds, but Allergan must grant us a non-exclusive license under any intellectual property rights Allergan may own related to our selected compounds to develop and commercialize our selected compounds outside of Allergan’s field of specified indications.

During the exclusivity period set forth in the agreement, 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. 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 Aptinyx approval at our sole discretion. The exclusivity period commences on the effective date of the agreement and ends on the third anniversary of the last day of the term of the agreement.

The Allergan Research Collaboration Agreement expires on the expiration of Allergan's options. The term for Allergan's options expires on February 24, 2021; provided that such period would be extended as needed to permit Aptinyx to provide a complete data package to Allergan for the Allergan selected compounds. The option period (and the research collaboration agreement) would terminate prior to expiration if and when Allergan exercises a third option under the research collaboration agreement. Allergan may terminate the Allergan Research Collaboration Agreement upon 60 days' written notice to us. Either party may terminate the agreement immediately upon written notice upon the other party's filing for protection under bankruptcy or insolvency laws. In the event we are in material breach of one or more of our material obligations under the agreement, then Allergan may terminate the agreement and the exclusivity period will remain in effect until a predetermined anniversary of the date that would have been the expiration date if the research term had run its full course without extension. Upon termination of the research collaboration agreement, the research program will terminate, rights to molecules that were previously optioned by Allergan will continue in effect, and all molecules, and associated data, for which Allergan has selected but not exercised an option will be returned to us and will no longer be subject to any Allergan rights.

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, where specialist capabilities are needed. 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 March 18, 2019, 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 pending U.S. patent application and one pending U.S. provisional patent application that relate to NYX-2925, and one pending U.S. patent application that relates 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 latest filed provisional patent application, and if any patents issue based on such pending applications, we expect such patents, if issued, to expire between 2034 and 2039.

### *NYX-458*

As of March 18, 2019, we own one issued U.S. patent, one pending U.S. patent application, and pending foreign counterpart patent applications, that relate to our product candidate, NYX-458. The issued U.S. patent is expected to expire in 2037. If we continue to pursue patent protection, and if any patents issue based on our pending applications, we expect such patents to expire in 2037.

### *Other compounds*

As of March 18, 2019, we own seven issued U.S. patents, thirteen pending U.S. patent applications, and pending and issued foreign counterpart patents and patent applications, as well as six international PCT patent applications and ten U.S. provisional patent applications, all of which generally relate to our efforts to develop other compounds in our NMDA<sub>r</sub> 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 of one or more of our related 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 2040.

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 21<sup>st</sup> 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, its safety in use and to establish the overall benefit/risk relationship of the product and 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, 2018 through September 30, 2019, the user fee for an application requiring clinical data, such as an NDA, is \$2,588,478. PDUFA also imposes an annual prescription drug product program fee for human drugs (\$309,915). 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 patent 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 three times the actual damages sustained by the government, plus mandatory 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, , 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 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 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. 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 in 2019 with a three-year transition period. 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 European Economic Area, or EEA, comprising the 28 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 and use of personal health data in the European Economic Area (EEA) is governed by the General Data Protection Regulation 2016/679 (or GDPR), which became effective May 25, 2018. 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 EU or the monitoring of the behavior of data subjects in the EU. The GDPR enhances data protection obligations for data controllers of personal data (including stringent requirements relating to the consent of data subjects, 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) and creates direct obligations on service providers acting as data processors. 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. 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. Moreover, the GDPR grants data subjects the right to claim material and non-material damages resulting from infringement of the GDPR. Given the breadth and depth of changes in data protection obligations, maintaining compliance with the GDPR, will require significant time, resources and expense, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

### ***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 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% (70% commencing 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 of up to an aggregate of \$165,786 per year (or up to an aggregate of \$1,105,241 per year for “knowing failures”), 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. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation through 2019.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently finalized regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Congress may consider other legislation to replace elements of the ACA. The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate.” Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plan, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to reduce the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” In July 2018, CMS announced that it is suspending further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program pending the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseparable feature of the Affordable Care Act, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the Affordable Care Act are invalid as well. The Texas District Court Judge, as well as the Trump Administration and CMS, have stated that the ruling will have no immediate effect, and on December 30, 2018

the Texas District Court Judge issued an order staying the judgment pending appeal. It is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act.

Congress also could consider additional legislation to repeal, replace, or further modify elements of the ACA. Thus, the full impact of the ACA, or any law replacing elements of it, and the political uncertainty regarding any repeal and replacement on the ACA, on our business remains unclear. Many of the details regarding the implementation of the ACA are yet to be determined, and at this time, it remains unclear the full effect that the ACA would have on our business. There have been judicial and Congressional challenges to the ACA, and we expect such challenges and amendments to continue in the future.

Moreover, in May 2018, the Trump administration released its “Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs,” or the Blueprint. The Blueprint contains 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. In addition, the Department of Health and Human Services, or HHS, released a Request for Information, or RFI, soliciting public input on ways to lower drug pricing. Together, the recommendations in the Blueprint and RFI, if enacted by Congress and HHS, could lead to changes to Medicare Parts B and D, including the transition of certain drugs covered under Part B to Part D or the offering of alternative purchasing options under the Competitive Acquisition Program that currently applies to selected drugs and biologics covered under Part B. In September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019. While most of the proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative, administrative and/or additional measures to control drug costs.

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 will remain in effect through 2027 unless additional congressional action is taken. 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 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**

As of March 18, 2019, we employed 63 full-time employees, including 48 in research and development and 15 in general and administrative, and no part-time employees. 21 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 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.aptinix.com](http://www.aptinix.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.aptinix.com](http://www.aptinix.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](http://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.aptinix.com](http://www.aptinix.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 a very limited operating history and 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 with a limited operating history, 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 short operating history as a company makes any assessment of our future success and viability 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.

***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. From our inception through December 31, 2018, we have received net proceeds of \$267.4 million from such transactions. As of December 31, 2018, our cash and cash equivalents were \$150.6 million. We have incurred net losses in each year since our inception, and we have an accumulated deficit of \$105.5 million as of December 31, 2018.

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 (deficit) 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.

***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 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, which are at various stages of clinical development. 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.

In July 2015, we entered into a research collaboration agreement, or Allergan Research Collaboration Agreement, with Allergan plc, or Allergan, pursuant to which we and Allergan have research, development, and commercial rights to compounds discovered using our discovery platform. Under the research collaboration, both we and Allergan have the right, exercisable during a specified period, to select an eligible compound for further investigation. Due to the terms of the Allergan Research Collaboration Agreement, we may not have the opportunity to select a desired eligible compound. We may also choose not to select an eligible compound based on the preliminary information available to us. As a result of such incomplete information or incorrect analysis by us, we may select an eligible compound that later proves to have less commercial potential than an alternative or none at all.

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;
- 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, 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, 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 NMDAr. 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.***

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. It is estimated that over 8.5 million people suffer from PTSD. 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. Furthermore, we may experience difficulties in subject enrollment in our clinical studies for a variety of other reasons, including:

- 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.

For instance, we have experienced and may continue to experience slower than what may be considered typical durations for subject enrollment as a result of our strict enrollment criteria in our painful DPN and fibromyalgia 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. 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:

- 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, 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:

- 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. 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 Adamas Pharmaceuticals Inc., Allergan plc, AmKor Pharma, Inc., Avanir Pharmaceuticals, Inc., Axsome Therapeutics, Inc., Biohaven Pharmaceutical Holding Co. Ltd., Cadent Therapeutics, Inc., Cerecor Inc., Eli Lilly and Company, Genentech Inc., Immune Pharmaceuticals 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., 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. 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 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, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal False Claims Act imposes civil penalties, including those from civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government;

- 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 executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact, or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services;
- 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 payments and other transfers of value and physician ownership and investment interests; and
- analogous state 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.

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, 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.

***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.***

Market acceptance and sales of our product candidates will depend on reimbursement policies and may be affected by healthcare reform measures. 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. 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.

***Recently enacted 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. In March 2010, President Obama signed into law the ACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry, and impose additional health policy reforms.

Among the provisions of the ACA of importance to our product candidates are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- 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;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the AKS, which include, among other things, new government investigative powers and enhanced penalties for non-compliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- the requirements under the federal open payments program and its implementing regulations;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Since its enactment, some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial, congressional, and executive challenges. As a result, there have been delays in the implementation of, and action taken to repeal or replace, certain aspects of the ACA. The U.S. Supreme Court has upheld certain key aspects of the legislation, including a tax-based shared responsibility payment imposed on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly known as the “individual mandate.” However, as a result of tax reform legislation passed in late December 2017, the individual mandate has been eliminated effective January 1, 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise.

Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies, or CSR, that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. In addition, the Centers for Medicare & Medicaid Services, or CMS, has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We continue to evaluate the effect that the ACA and its possible repeal and replacement has on our business.

Moreover, in May 2018, the Trump administration released its “Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs,” or the Blueprint. The Blueprint contains 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. In addition, HHS released a Request for Information, or RFI, soliciting public input on ways to lower drug pricing. Together, the recommendations in the Blueprint and RFI, if enacted by Congress and HHS, could lead to changes to Medicare Parts B and D, including the transition of certain drugs covered under Part B to Part D or the offering of alternative purchasing options under the Competitive Acquisition Program that currently applies to selected drugs and biologics covered under Part B. In September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019. While most of the proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative, administrative and/or additional measures to control drug costs.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of 2% per fiscal year through 2027. 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, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and in 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.

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 of 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 depend on our collaboration with Allergan and may depend on collaborations with third parties for the research, development, and commercialization of certain of the 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.***

In July 2015, we entered into the Allergan Research Collaboration Agreement, focused on the research and discovery of small molecules that modulate NMDARs. Under the Allergan Research Collaboration Agreement, Allergan and we may exercise the right to pick certain product candidates from a pool of eligible compounds (which were selected based upon the results of a mutually agreed set of screening assays of molecules from our drug discovery platform) in alternating fashion. 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. Allergan may also exercise its option to acquire up to two more of its selected compounds and must pay an option exercise fee for each such compound. The collaboration involves a complex allocation of rights. Under this agreement, each time Allergan exercises its option right with respect to a particular compound, Allergan will exclusively own the intellectual property rights specific to such compound and we will not be permitted to develop or commercialize such compound. When Allergan exercises one of its options with respect to a particular compound, we will not be entitled to any milestones, royalties, or other downstream revenue with respect to that compound other than the \$1.0 million exercise fee. When Allergan exercises its option on a compound that ultimately generates any revenue, we are not entitled to receive any of the resulting revenue

from such product candidate and, as a result, may not realize the economic benefits of a compound we generated from our discovery platform. We cannot provide any assurance that this collaboration will enhance our business or that we will achieve significant benefits from the collaboration. Moreover, we cannot provide any assurance with respect to the success of the collaboration. See “Business—Research collaboration agreement with Allergan” for more detail.

We may seek third-party collaborators for the research, development, and commercialization of certain of the 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. For example, under the Allergan Research Collaboration Agreement, Allergan funds a certain amount for costs associated with our medicinal chemistry, screening, and profiling efforts;
- 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, including our research collaboration with Allergan, 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 Allergan Research Collaboration Agreement, during the research term defined therein, we cannot, directly or indirectly, whether alone, or with a third party, engage in any activities to identify, generate, discover, or develop small-molecule compounds that modulate NMDArs, including any collaboration compounds, except as set forth in the agreement. In addition, during the exclusivity period defined 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. 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 the 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.

Further, our collaboration with Allergan is supervised by a joint steering committee, or JSC. Subject to limitations specified in the agreement, if the JSC is unable to make a decision by consensus and the parties are unable to resolve the issue after referring the matter to designated executive officers of the parties, then such disputed matter shall remain deadlocked until mutual agreement, provided that each party will have the right to make the final decision with respect to any matter concerning its respective selected compounds. These exclusivity and governance 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 have entered into a sponsored research agreement with Northwestern University, or Northwestern, through which Northwestern furnishes the laboratory facilities and equipment necessary to conduct certain research projects and related clinical studies. 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:

- 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. For example, the sponsored research agreement with Northwestern may be terminated by either party upon 60 days' written notice to the other party. 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 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 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 currently have no issued patents covering our clinical-stage product candidate NYX-458. 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.

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.

***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 the patent families related to NYX-458, as well as for many of the patent families that we own, the relevant statutory deadlines have not yet expired. Thus, for each of the patent families that we believe provide coverage for our lead product candidates, 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, 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.

***Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

As is the case with other biotechnology and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology and pharmaceutical industries 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 reform legislation: the Leahy-Smith America Invents Act. The America Invents Act includes a number of significant changes to U.S. patent law. After March 2013, under the America Invents Act, the United States transitioned to a first-inventor-to-file system in which, assuming that other requirements for patentability are met, the first-inventor-to-file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The America Invents Act also includes provisions that affect the way patent applications will be prosecuted and that may also affect patent 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 our patent applications, all of which could have a material adverse effect on our business and financial condition.

In addition, U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. The full impact of these decisions is not yet known. For example, on March 20, 2012, in *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, the Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patent eligible subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Court held that claims to isolated genomic DNA are not patent eligible, but claims to complementary DNA molecules are patent eligible because they are not a natural product. The effect of the decision on patents for other isolated natural products is uncertain. However, on March 4, 2014, the USPTO issued a memorandum to patent examiners providing guidance for examining claims that recite laws of nature, natural phenomena or natural products under the *Myriad* and *Prometheus* decisions. This guidance did not limit the application of *Myriad* to DNA but rather applied the decision to other natural products.

In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on these and other 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 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 will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.***

As of March 18, 2019, we had 63 full-time employees and no part-time employees. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of technology research, product development and manufacturing, clinical affairs, regulatory affairs and, if any of our product candidates are submitted for or receive marketing approval, sales, marketing and distribution. To manage our anticipated development and expansion, we must continue to implement and improve our managerial, operational, and financial systems, expand our facilities, and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional 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.

We are highly dependent on our management, scientific and medical personnel, including our Chief Executive Officer, Norbert G. Riedel, Ph.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 \$5.0 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 increased costs as a result of operating as a public company, and our management team is required to devote substantial time to new compliance initiatives.***

As a public company, we incur significant legal, accounting, and other expenses that we did not incur as a private company 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 will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. 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 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 will need to continue to dedicate internal resources, potentially engage outside consultants, and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe 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.

***If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could result in sanctions or other penalties that would harm our business.***

We are subject to the reporting requirements of the Securities Exchange Act of 1934, or the Exchange Act, the Sarbanes-Oxley Act, and the rules and regulations of The Nasdaq Stock Market. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal controls over financial reporting. Commencing with our fiscal year ending December 31, 2019, we must perform system and process design evaluation and testing of the effectiveness of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Form 10-K filing for that year, as required by Section 404 of the Sarbanes-Oxley Act. This will require that we incur substantial additional professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts. Prior

to our IPO, we were never required to test our internal controls within a specified period and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

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. 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, 2018, we had federal and state net operating loss, or NOL, carryforwards of \$97.3 million and \$9.2 million, respectively. Of the \$97.3 million federal NOL carryforwards, \$48.9 million will begin to expire in 2035 and the remaining \$48.4 million has an indefinite carryforward period as a result of the TCJA. However, NOLs arising in tax years beginning after December 31, 2017, NOL carryforwards will be limited to 80% of taxable income. Under Section 382 of the Code, 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 2018, we performed a detailed analysis of historical and current Section 382 ownership changes that may limit the utilization of NOL carryforwards. Except for approximately \$7.1 million of NOLs arising prior to May 2016, we expect the entire remaining federal NOL carryforward will not be subject to limitations under Section 382 of the Code. 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 of the Code 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. 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 and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.***

Earthquakes or other natural disasters 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 may 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. 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, 2018, our common stock's sales price on The Nasdaq Global Select Market ranged from a low of \$16.15 to a high of \$31.85, and on January 16, 2019, following announcement of our Phase 2 painful DPN study results, the closing price of a share of our common stock was \$5.98. The market price of our common stock may fluctuate significantly in response to a number of factors, most of which we cannot control, including, among others:

- plans for, progress of, or results from preclinical studies and clinical studies of our product candidates;
- the failure of the FDA to approve our product candidates;
- announcements of new products, technologies, commercial relationships, acquisitions, or other events by us or our competitors;
- the success or failure of other therapies for disorders of the brain and nervous system;
- regulatory or legal developments in the United States and other countries;
- failure of our product candidates, if approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- general economic, industry, and market conditions and overall fluctuations in U.S. equity markets;
- variations in our quarterly operating results or those of companies that are perceived to be similar to us;
- changes in our financial guidance or securities analysts' estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors, and significant stockholders;
- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities;
- market conditions in the pharmaceutical and biotechnology sectors; and
- other risks and uncertainties described in these risk factors.

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 33,562,211 shares outstanding as of March 18, 2019, our executive officers, directors, five percent stockholders and their affiliates beneficially owned approximately 60% 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, Partner Fund Management, Adams Street, New Leaf Ventures, Longitude, and Frazier, represent beneficial ownership, in the aggregate, of approximately 60% 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 8,132,506 shares issued or reserved for issuance 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 18, 2019, the holders of approximately 20,306,497 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 an exclusive forum provision, 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 the United States District Court for the Northern District of Illinois is the exclusive forum 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. 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. Some companies that have adopted similar federal district court forum selection provisions are currently subject to a suit in the Court of Chancery of the State of Delaware brought by stockholders who assert that the federal district court forum selection provision is not enforceable. We recognize that the federal district court forum selection clause 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 Illinois. Additionally, the 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. 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.

In *Sciabacucchi v. Salzberg*, C.A. No. 2017-0931-JTL (Del. Ch.), some companies that have adopted similar federal district court forum selection provisions were sued in the Court of Chancery of the State of Delaware by stockholders who assert that those federal district court forum selection provisions are not enforceable. On December 19, 2018, Court of Chancery issued a decision in *Sciabacucchi* declaring that provisions in certificates of incorporation of Delaware companies that purport to require claims under the Securities Act of 1933, as amended (the "Securities Act"), be brought in federal court are ineffective and invalid under Delaware law. On February 12, 2019, the Delaware Supreme Court held that the *Sciabacucchi* decision is not final and appealable until the Court of Chancery rules on an outstanding application for attorneys' fees. Unless and until the Court of Chancery's decision in *Sciabacucchi* is reversed or otherwise abrogated, we do not intend to enforce our Federal Forum Provision designating the Northern District of Illinois as the exclusive forum for Securities Act claims. In the event that the Delaware Supreme Court affirms the Court of Chancery's *Sciabacucchi* decision or otherwise makes a determination that provisions such as the Federal Forum Provision are invalid, our Board of Directors intends to amend promptly our bylaws to remove the Federal Forum Provision. Such amendment could cause us to incur additional costs, which could have an adverse effect on our business, financial condition or results of operations.

***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 18, 2019, we had approximately 163 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.

### **Purchase of Equity Securities**

We did not purchase any of our equity securities during the period covered by 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 affiliates.

As of December 31, 2018, none of the net offering proceeds from the IPO have been used. We are holding the net proceeds from the IPO in cash and cash equivalents. 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.





through functional magnetic resonance imaging, or fMRI. NYX-2925 also showed favorable corresponding trends of improvement on the secondary measures including pain, fibromyalgia impact, and cognition. We expect to complete this exploratory study and report data in the first half of 2019. Based on the results from the interim analysis we expect to initiate a larger Phase 2 study in patients with fibromyalgia in the second half of 2019.

NYX-783 is in development for the treatment of post-traumatic stress disorder, or PTSD. NYX-783 has been evaluated in Phase 1 clinical development and has been shown to be well tolerated, with no drug related serious adverse events, and to have a dose dependent, predictable, and linear pharmacokinetic profile. We recently initiated a Phase 2 clinical study of NYX-783 in patients with PTSD. This first-in-patient study is a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of NYX-783 in approximately 144 patients with PTSD. We expect to report data from this study in the first half of 2020.

We are currently evaluating the safety, tolerability, and pharmacokinetics of NYX-458 in a Phase 1 study in healthy volunteers, which we expect to complete in the first half of 2019. We intend to develop NYX-458 for the treatment of cognitive impairment associated with Parkinson's disease.

We believe that our available funds will be sufficient to fund our operations for at least the next twelve 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. 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 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.

## **Financial operations overview**

### ***Collaboration and grant revenue***

We have not generated any revenue from product sales. Our revenue to date has been primarily derived from a research collaboration agreement with Allergan; 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., or Naurex, prior to the spin-out of Aptinyx; and research and development grants from the U.S. government which have no repayment or royalty obligations. All grants awarded to us were completed prior to December 31, 2018. The development services agreement with Allergan was terminated in October 2016. Therefore, we have not generated any revenues under this agreement since October 2016 and do not expect to generate revenues in the future under this agreement.

### ***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, 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. We are also unable to predict when, if ever, material net cash inflows will commence from sales of our products, if approved. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty related to:

- 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;
- decisions by regulatory authorities related to our product candidates;
- 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 personnel-related costs, including stock-based compensation for employees performing functions other than research and development, rent, general overhead as well as insurance and other professional fees such as legal, consulting, accounting, and audit services.

In the future, we expect that our general and administrative expenses will increase as we increase our headcount to support our continued 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, 2018 and 2017**

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

	Year ended December 31,		Increase (Decrease)
	2018	2017	
Collaboration and grant revenue	\$ 6,574	\$ 4,962	\$ 1,612
Operating expenses:			
Research and development	48,788	31,644	17,144
General and administrative	12,674	5,551	7,123
Total operating expenses	61,462	37,195	24,267
Loss from operations	(54,888)	(32,233)	22,655
Other income	1,607	165	1,442
Net loss and comprehensive loss	\$ (53,281)	\$ (32,068)	\$ 21,213

### ***Collaboration and grant revenue***

Revenue was \$6.6 million for the year ended December 31, 2018, compared to \$5.0 million for the year ended December 31, 2017. The net increase of \$1.6 million was primarily the result of the following changes:

- approximately \$0.6 million increase reflecting incremental work performed under our research and development grants from the U.S. government associated with preclinical studies towards NYX-458. We do not expect to generate grant revenues in the future; and
- \$1.0 million increase due to Allergan's exercise of its option in May 2018 to acquire exclusive rights to develop and commercialize AGN-241751 under the research collaboration agreement with Allergan.

### ***Research and development expenses***

The following table summarizes our research and development expenses incurred during the years ended December 31, 2018 and 2017 (in thousands):

	Year ended December 31,		Increase (Decrease)
	2018	2017	
NYX-2925	\$ 21,240	\$ 10,257	\$ 10,983
NYX-783	3,823	2,424	1,399
NYX-458	3,245	1,746	1,499
Preclinical research and discovery programs	7,645	6,960	685
Personnel and related costs	12,835	10,257	2,578
Total research and development expenses	\$ 48,788	\$ 31,644	\$ 17,144

Research and development expenses were \$48.8 million for the year ended December 31, 2018, compared to \$31.6 million for the year ended December 31, 2017. The increase of \$17.2 million was primarily due to the following:

- approximately \$11.0 million increase for clinical, regulatory, and drug product costs related to the development of NYX-2925, including enrollment efforts in our Phase 2 clinical study in patients with painful DPN, ongoing enrollment in an exploratory clinical study in patients with fibromyalgia, and two Phase 1 exploratory pharmacodynamic clinical studies that we commenced and completed in 2018;
- approximately \$1.4 million increase for clinical, regulatory, and drug-product costs for work initiated in the fourth quarter of 2017 related to the ongoing development of NYX-783 for the treatment of PTSD;
- approximately \$1.5 million increase for external research and development costs, IND-enabling activities, and Phase 1 clinical study costs for work initiated in the fourth quarter of 2017 related to ongoing development of NYX-458 for the treatment of Parkinson's disease cognitive impairment;
- approximately \$0.6 million increase for costs associated with our internal preclinical research efforts and sponsored research activities with academic institutions; and
- approximately \$2.6 million increase for costs related to employee compensation and related support, including \$0.5 million of additional stock-based compensation expense, due to increased headcount.

### ***General and administrative expenses***

General and administrative expenses were \$12.7 million for the year ended December 31, 2018, compared to \$5.6 million for the year ended December 31, 2017. The increase of \$7.1 million was primarily driven by \$3.3 million for increased costs related to employee compensation, including \$1.9 million of additional stock-based compensation expense, due to increased headcount and \$3.1 million of increased professional fees spent to support ongoing business operations and to comply with obligations associated with being a publicly traded company.

### ***Other income***

We recorded \$1.6 million of other income for the year ended December 31, 2018, compared to \$0.2 million for the year ended December 31, 2017. This was due to increased interest income earned on our cash and cash equivalents.

## **Liquidity and capital resources**

From our inception through December 31, 2018, 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. 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.

As of December 31, 2018, we had cash and cash equivalents of \$150.6 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:

- advance the clinical development of our lead product candidates;
- continue the research and development of our preclinical product candidates;
- seek to identify and develop additional product candidates;
- seek marketing approvals for any of our product candidates for which we successfully complete clinical development;
- develop and expand our sales, marketing, and distribution capabilities for our product candidates for which we obtain marketing approval;
- scale up our manufacturing processes and capabilities to support our ongoing preclinical activities and clinical studies of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;
- maintain, expand, and protect our intellectual property portfolio;
- expand our operational, financial, and management systems and increase personnel to support our clinical development, manufacturing, and commercialization efforts; and
- increase our product liability and clinical trial insurance coverage as we initiate our clinical studies and commercialization efforts.

## Outlook

As of December 31, 2018, we had cash and cash equivalents of \$150.6 million. We believe that our available funds will be sufficient to fund our operations for at least the next twelve 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. We will continue to require additional capital to develop our product candidates and fund operations for the foreseeable future, 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. 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 pace and results of our preclinical and clinical development efforts and the prioritization of our research and development pipeline. 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,	
	2018	2017
Net cash provided by (used in):		
Operating activities	\$ (47,448)	\$ (32,735)
Investing activities	(407)	(1,577)
Financing activities	106,374	109,968
<b>Net increase in cash, cash equivalents and restricted cash</b>	<b>\$ 58,519</b>	<b>\$ 75,656</b>

### Net cash used in operating activities

During the year ended December 31, 2018, our cash used in operating activities was primarily due to our net loss of \$53.3 million as we incurred increased external research and development costs associated with our clinical studies during the year ended December 31, 2018 and increased general and administrative costs, partially offset by non-cash charges of \$3.8 million, consisting primarily of \$3.3 million in stock-based compensation and \$0.5 million in depreciation and amortization. Net cash provided by changes in our operating assets and liabilities consisted of a \$2.3 million change in accrued expenses and other liabilities, accounts payable and accounts receivable offset by a \$0.3 million use of cash driven by a change in prepaid expenses and other assets.

During the year ended December 31, 2017, our cash used in operating activities was primarily due to our net loss of \$32.1 million, partially offset by non-cash charges of \$1.3 million, consisting primarily of \$0.9 million in stock-based compensation and \$0.4 million in depreciation and amortization. Net cash used in changes in our operating assets and liabilities consisted of a \$1.9 million use of cash driven by changes in prepaid expenses and other assets, accounts receivable, accounts payable and accrued expenses and other liabilities.

### *Net cash used in investing activities*

Net cash used in investing activities was \$0.4 million during the year ended December 31, 2018 compared to \$1.6 million during the year ended December 31, 2017. The decrease in 2018 from 2017 related to the investments made in building out our leased corporate office in 2017, as well as the timing of procurement of specific laboratory equipment used in our research and development activities.

### *Net cash provided by financing activities*

Net cash provided by financing activities was \$106.4 million during the year ended December 31, 2018, consisting primarily of \$109.5 million of IPO proceeds, net of underwriting discounts and commissions offset by \$3.0 million of offering costs related to our IPO, and additional financing costs of \$0.2 million related to our Series B convertible preferred stock financing that closed in December 2017.

Net cash provided by financing activities was \$110.0 million during the year ended December 31, 2017, consisting of proceeds of \$40.0 million received from the issuance of our Series A-2 convertible preferred stock and proceeds of \$70.0 million received from the issuance of our Series B convertible preferred stock.

### **Contractual obligations and other commitments**

We enter into contracts in the normal course of business with contract research organizations for clinical studies, preclinical research studies and testing, manufacturing, and other services and products for operating purposes. These contracts generally are cancelable at any time by us, generally upon 30 days prior written notice, and therefore these payments are not included in our table of contractual obligations.

The following table summarizes our contractual obligations as of December 31, 2018 (in thousands):

Contractual Obligations:	Payments due by period					Total
	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years		
Operating leases	\$ 848	\$ 1,731	\$ 587	\$ —	\$	3,166
Total contractual obligations	\$ 848	\$ 1,731	\$ 587	\$ —	\$	3,166

### **Off-balance sheet arrangements**

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

### **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 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 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) the last day of the fiscal year following the fifth anniversary of the date of the completion of our IPO in June 2018; (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 99.

## **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**

The Company has 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 Company files or submits 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.

The Company's management, with the participation of the Company's Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of the Company's disclosure controls and procedures as of December 31, 2018. 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 the Company's disclosure controls and procedures as of December 31, 2018, the Company's Chief Executive Officer and Chief Financial Officer concluded that, as of such date, the Company's disclosure controls and procedures were effective at the reasonable assurance level.

### **Management's Annual Report on Internal Control Over Financial Reporting**

This Annual Report on Form 10-K does not include a report of management's assessment regarding our internal control over financial reporting or an attestation report of our registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public 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, 2018 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 2019 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 2019 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 2019 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 2019 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 2019 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 and Comprehensive Loss

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

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.



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

### **Opinion on the Financial Statements**

We have audited the accompanying balance sheets of Aptinix Inc. (the "Company") as of December 31, 2018 and 2017, the related statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows, for each of the two years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, 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 21, 2019

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

Aptinyx Inc.

**Balance Sheets**  
(In thousands, except per share data)

	December 31, 2018	December 31, 2017
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 150,637	\$ 92,136
Restricted cash	252	—
Accounts receivable	578	937
Prepaid expenses and other current assets	1,784	1,960
Total current assets	153,251	95,033
Other assets	673	473
Property and equipment, net	1,690	1,816
Total assets	<u>\$ 155,614</u>	<u>\$ 97,322</u>
<b>Liabilities, convertible preferred stock, and stockholders' equity (deficit)</b>		
Current liabilities:		
Accounts payable	\$ 1,889	\$ 1,537
Accrued expenses and other current liabilities	3,996	2,835
Total current liabilities	5,885	4,372
Other long-term liabilities	418	282
Total liabilities	<u>\$ 6,303</u>	<u>\$ 4,654</u>
Commitments and contingencies (see Note 15)		
Convertible preferred stock:		
Convertible preferred stock, Series A-1, \$0.01 par value, no shares and 151,773 shares authorized, issued and outstanding at December 31, 2018 and December 31, 2017, respectively	—	22,650
Convertible preferred stock, Series A-2, \$0.01 par value, no shares and 173,453 shares authorized, issued and outstanding at December 31, 2018 and December 31, 2017, respectively	—	39,979
Convertible preferred stock, Series B, \$0.01 par value, no shares and 234,955 shares authorized, issued and outstanding as of December 31, 2018 and December 31, 2017, respectively	—	69,757
Stockholders' equity (deficit):		
Preferred stock, \$0.01 par value, 10,000 and no shares authorized as of December 31, 2018 and December 31, 2017, respectively; no shares issued and outstanding as of December 31, 2018 and December 31, 2017, respectively	—	—
Common stock, \$0.01 par value, 150,000 shares authorized, 33,341 issued and outstanding as of December 31, 2018 and 900,000 shares authorized, 5,342 issued and outstanding as of December 31, 2017	333	53
Additional paid-in capital	254,516	12,486
Accumulated deficit	(105,538)	(52,257)
Total stockholders' equity (deficit)	<u>\$ 149,311</u>	<u>\$ (39,718)</u>
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	<u>\$ 155,614</u>	<u>\$ 97,322</u>

See accompanying notes to financial statements.

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

	Year ended	
	December 31,	
	2018	2017
Collaboration and grant revenue	\$ 6,574	\$ 4,962
Operating expenses:		
Research and development	48,788	31,644
General and administrative	12,674	5,551
Total operating expenses	<u>61,462</u>	<u>37,195</u>
Loss from operations	(54,888)	(32,233)
Other income	1,607	165
Net loss and comprehensive loss	<u>\$ (53,281)</u>	<u>\$ (32,068)</u>
Net loss per share attributable to common stockholders, basic and diluted	<u>\$ (2.64)</u>	<u>\$ (6.17)</u>
Weighted-average number of common shares outstanding, basic and diluted	<u>20,199</u>	<u>5,196</u>

See accompanying notes to financial statements.

**Aptinyx Inc.**  
**Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)**

(in thousands)

	Series A-1		Series A-2		Series B		Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	convertible preferred stock Amount	Shares	convertible preferred stock Amount	Shares	convertible preferred stock Amount	Shares	Amount			
<b>Balance at January 1, 2017</b>	151,773	\$ 22,650	—	\$ —	—	\$ —	5,049	\$ 50	\$ 11,588	\$ (20,189)	\$ (8,551)
Issuance of Series A-2 convertible preferred stock, net of issuance costs of \$21	—	—	173,453	39,979	—	—	—	—	—	—	—
Issuance of Series B convertible preferred stock, net of issuance costs of \$243	—	—	—	—	234,955	69,757	—	—	—	—	—
Issuance of common stock upon vesting of restricted stock awards	—	—	—	—	—	—	293	3	(3)	—	—
Stock-based compensation	—	—	—	—	—	—	—	—	901	—	901
Net loss	—	—	—	—	—	—	—	—	—	(32,068)	(32,068)
<b>Balance at December 31, 2017</b>	151,773	\$ 22,650	173,453	\$ 39,979	234,955	\$ 69,757	5,342	\$ 53	\$ 12,486	\$ (52,257)	\$ (39,718)
Issuance of common stock upon vesting of restricted stock awards	—	—	—	—	—	—	293	3	(3)	—	—
Stock-based compensation	—	—	—	—	—	—	—	—	3,318	—	3,318
Conversion of preferred stock upon IPO	(151,773)	(22,650)	(173,453)	(39,979)	(234,955)	(69,757)	20,306	203	132,183	—	132,386
Issuance of common stock upon IPO, net of underwriters' discount and other offering costs \$3,012	—	—	—	—	—	—	7,360	74	106,431	—	106,505
Issuance of common stock upon exercise of stock options	—	—	—	—	—	—	40	—	101	—	101
Net loss	—	—	—	—	—	—	—	—	—	(53,281)	(53,281)
<b>Balance at December 31, 2018</b>	—	\$ —	—	\$ —	—	\$ —	33,341	\$ 333	\$ 254,516	\$ (105,538)	\$ 149,311

See accompanying notes to financial statements.



**Aptinyx Inc.**  
**Statements of Cash Flows**  
(in thousands)

	<b>Year Ended</b>	
	<b>December 31,</b>	
	<b>2018</b>	<b>2017</b>
<b>Cash flows from operating activities:</b>		
Net loss	\$ (53,281)	\$ (32,068)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization expense	457	405
Stock-based compensation expense	3,318	901
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(260)	(1,355)
Accounts receivable	359	(448)
Accounts payable	418	(124)
Accrued expenses and other liabilities	1,541	(46)
Net cash used in operating activities	<u>(47,448)</u>	<u>(32,735)</u>
<b>Cash flows from investing activities:</b>		
Purchases of property and equipment	(407)	(1,577)
Net cash used in investing activities	<u>(407)</u>	<u>(1,577)</u>
<b>Cash flows from financing activities:</b>		
Proceeds from issuance of Series A-2 convertible preferred stock, net of issuance costs	—	39,979
Payment of deferred issuance costs associated with Series B convertible preferred stock financing	(232)	—
Proceeds from issuance of Series B convertible preferred stock, net of issuance costs	—	69,989
Proceeds from stock options exercised	101	—
Proceeds from initial public offering, net of underwriters' discounts	109,517	—
Payment of deferred offering costs	(3,012)	—
Net cash provided by financing activities	<u>106,374</u>	<u>109,968</u>
Net increase in cash, cash equivalents and restricted cash	58,519	75,656
Cash, cash equivalents and restricted cash, at beginning of period	92,609	16,953
Cash, cash equivalents and restricted cash, at end of period	<u>\$ 151,128</u>	<u>\$ 92,609</u>
<b>Supplemental disclosure of non-cash investing and financing activities:</b>		
Series B convertible preferred stock financing costs not yet paid	\$ —	\$ 232

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 \$105.5 million as of December 31, 2018. 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.

As of December 31, 2018, the Company had cash and cash equivalents of \$150.6 million which 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.

**Initial public offering**

On June 20, 2018, the Company’s registration statement on Form S-1 (File No. 333-225150) relating to the initial public offering (“IPO”) of its common stock became effective and on June 25, 2018, the IPO closed. Pursuant to the IPO, the Company issued and sold 7,359,998 shares of common stock at a public offering price of \$16.00 per share, which included 959,999 shares sold pursuant to the exercise of the underwriters’ option to purchase additional shares. The Company received net proceeds of \$106.5 million after deducting underwriting discounts and commissions and other offering costs of \$3.0 million. The shares began trading on the Nasdaq Global Select Market on June 21, 2018. Upon the closing of the IPO, all of the Company’s outstanding shares of convertible preferred stock automatically converted into 20,306,497 shares of common stock at the applicable conversion ratio.

On June 7, 2018, the Company effected a one-for-27.58621 reverse stock split of its issued and outstanding shares of common stock and a proportional adjustment to the existing conversion ratios for each series of the Company's redeemable convertible preferred stock (see Note 10). Accordingly, all share and per share amounts for all periods presented in the financial statements have been adjusted retroactively, where applicable, to reflect this reverse stock split and adjustment of the preferred stock conversion ratios.

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, 2018, no shares of preferred stock were issued or outstanding.

**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 issued accounting pronouncements**

In February 2016, the Financial Accounting Standards Board (“FASB”) issued Accounting Standards Update (“ASU”) No. 2016-02, *Leases (Topic 842)* (“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. In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements* (“ASU 2018-11”), which offers a transition option to entities adopting ASC 842. Under ASU 2018-11, entities can elect to apply ASC 842 using a modified-retrospective adoption approach resulting in a cumulative effect adjustment to accumulated deficit at the beginning of the year in which the new lease standard is adopted, rather than adjustments to the earliest comparative period presented in their financial statements. The new standard will be effective for the Company beginning after December 15, 2019, and early adoption is permitted. The Company is currently evaluating the potential impact ASC 842 may have on its financial statements.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* (“ASU 2014-09”), which supersedes nearly all existing revenue recognition guidance. The core principle of ASU 2014-09 is to recognize revenues when promised goods or services are transferred to customers in an amount that reflects the consideration to which an entity expects to be entitled for those goods or services. ASU 2014-09 defines a five-step process to achieve this core principle and, in doing so, more judgment and estimates may be required within the revenue recognition process than are required under existing GAAP. The standard is effective for annual periods, including interim periods within those fiscal years, beginning after December 15, 2018, using either of the following transition methods: (i) a full retrospective approach reflecting the application of the standard in each prior reporting period with the option to elect certain practical expedients, or (ii) a retrospective approach with the cumulative effect of initially adopting ASU 2014-09 recognized at the date of adoption (which includes additional footnote disclosures).

The Company will adopt ASC 606 effective January 1, 2019 using the modified retrospective method which requires that any cumulative effect of initially applying ASC 606 be recognized as an adjustment to the opening balance of accumulated deficit on the date of adoption. The Company has concluded that the Research Collaboration Agreement with Allergan (see Note 4) was the only material contract still in process as of the adoption date. The Company has identified that the contract includes the following promised goods and/or services: (i) access to research licenses, (ii) performing research and development activities, and (iii) participating in a joint steering committee. The Company has concluded that, individually, these promised goods and/or services are not distinct, and therefore represent a single combined performance obligation that will be satisfied over-time. The Company is substantially complete with its assessment, and does not expect the adoption of ASC 606 to have a material impact on its financial position, results of operations or cash flows. Upon adoption, the Company expects to disaggregate revenue from the Research Collaboration Agreement from income earned under government grants which the Company has concluded fall outside of the scope of ASC 606.

### **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.

#### ***Revenue recognition***

Revenue is recognized when all terms and conditions of the agreements have been met, including that persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed or determinable and collectability is reasonably assured.

The Company is reimbursed for certain costs incurred on specified research projects under the terms and conditions of a Research Collaboration Agreement that are reported within collaboration and grant revenue (as discussed in Note 4) in the statements of operations and comprehensive loss. The amounts of the reimbursements are recorded as revenues on a gross basis in accordance with ASC 605-45—*Revenue Recognition—Principal Agent Consideration*. The core principle is that the entity should recognize revenue to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. ASC 605-45 specifies various indicators that support the reporting of revenue on a gross basis. As the Company is considered the primary obligor, is exposed to credit risk, and has discretion in changing and selecting the supplier, the Company recognizes these reimbursements on a gross basis. The related expenses are primarily recorded within research and development expenses in the statements of operations and comprehensive loss.

The Company is also reimbursed for certain costs associated with government grants that provide funding for certain types of expenditures in connection with research and development activities over a contractually-defined period. Revenue related to government grants is recognized in the period during which the related costs are incurred and the related services are rendered, provided that the applicable performance obligations under the government grants have been met. The revenue is reported on a gross basis within collaboration and grant revenue and the related expenses are recorded within both general and administrative expenses and research and development expenses in the statements of operations and comprehensive loss.

### *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, 2018 and 2017, one research collaborator, Allergan plc (“Allergan”) represented 75% and 80%, respectively, of the Company’s revenues (see Note 4). The associated accounts receivable were approximately \$0.6 million and \$0.6 million at December 31, 2018 and 2017, respectively. The remaining accounts receivable as of December 31, 2017 relate to the Company’s grants with the U.S. government. 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, 2018 and 2017.

### *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,	
	2018	2017
Cash and cash equivalents	\$ 150,637	\$ 92,136
Short-term and long-term restricted cash	491	473
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	\$ 151,128	\$ 92,609

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, 2018 or 2017.

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

***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, 2018 and 2017.

***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.

### ***Convertible preferred stock***

The Company has applied the guidance in ASC 480-10-S99-3A, *SEC Staff Announcement: Classification and Measurement of Redeemable Securities* and has therefore classified the Series A-1, Series A-2 and Series B convertible preferred stock (Note 10) as mezzanine equity. The convertible preferred stock is recorded outside of stockholders' deficit because, in the event of certain deemed liquidation events considered not solely within the Company's control, such as a merger, acquisition and sale of all or substantially all of the Company's assets, the convertible preferred stock will become redeemable at the option of the holders. In the event of a change of control of the Company, proceeds received from the sale of such shares will be distributed in accordance with the liquidation preferences set forth in the Company's Amended and Restated Certificate of Incorporation. The Company has determined not to adjust the carrying values of the convertible preferred stock to the liquidation preferences of such shares because of the uncertainty of whether or when such an event would occur. As described in Note 1, all previously outstanding convertible preferred stock was converted to common stock upon the completion of the Company's IPO in June 2018.

### ***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. 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, 2018 and 2017, 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 2018 or 2017.

### ***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 and comprehensive loss.

### ***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”), focused on the research and discovery of small molecules that modulate NMDARs. The collaboration is supervised by a Joint Steering Committee (“JSC”) comprised of an equal number of representatives from both the Company and Allergan. Under the terms of the agreement, Allergan will pay the Company \$1.0 million for each option exercised by Allergan. Under the terms of the agreement, the RCA will terminate upon the earlier of a predetermined anniversary of the RCA or on the date on which Allergan exercises three options to acquire molecules from a pool of eligible compounds.

On May 16, 2018, Allergan exercised its option to acquire exclusive rights to develop and commercialize AGN-241751 within a predefined set of indications. During the year ended December 31, 2018, the Company recognized the \$1.0 million non-refundable milestone payment within collaboration and grant revenue in the statements of operations and comprehensive loss as there were no remaining performance obligations associated with the optioned compound.

Costs between the Company and Allergan with respect to each party’s share of development costs that have been incurred pursuant to the RCA are substantially recorded within research and development in the accompanying statements of operations and comprehensive loss. Reimbursable expenses under the RCA include chemistry, discovery, screening, and profiling efforts around novel NMDAR modulators from the Company’s discovery platform as well as salary of full-time employees at a fixed annual rate for each individual assigned to those efforts, consistent with oversight and guidance of the JSC. Such costs for each compound are considered reimbursable up until the point that the compound is selected by one of the collaboration parties. None of the costs reimbursed by Allergan in any period presented were directly related to the Company’s lead product candidates, NYX-2925, NYX-783, and NYX-458, which the Company selected under the collaboration.

During each of the years ended December 31, 2018 and 2017, the Company recorded expenses of \$7.9 million for certain development activities in accordance with the terms of the RCA of which 50% was reimbursed by Allergan. The Company received reimbursements of \$3.9 million during each of the years ended December 31, 2018 and 2017, which were reported within collaboration and grant revenue in the statements of operations and comprehensive loss.

#### 5. Fair value measurements

Assets measured at fair value as of December 31, 2018 are as follows (in thousands):

	December 31, 2018	Level 1	Level 2	Level 3
<b>Assets</b>				
Money market funds, included in cash and cash equivalents	\$ 150,151	\$ 150,151	\$ —	\$ —
Money market funds, included in restricted cash	\$ 252	\$ 252	—	—
Money market funds, included in other assets	239	239	—	—
	\$ 150,642	\$ 150,642	\$ —	\$ —



Assets measured at fair value as of December 31, 2017 are as follows (in thousands):

	December 31, 2017	Level 1	Level 2	Level 3
<b>Assets</b>				
Money market funds, included in cash and cash equivalents	\$ 89,553	\$ 89,553	\$ —	\$ —
Money market funds, included in other assets	317	317	—	—
	<u>\$ 89,870</u>	<u>\$ 89,870</u>	<u>\$ —</u>	<u>\$ —</u>

## 6. Prepaid expenses and other current assets

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

	As of December 31,	
	2018	2017
Prepaid clinical	\$ 728	\$ 1,718
Prepaid insurance	673	137
Other prepaid expenses and current assets	383	105
Total prepaid expenses and other current assets	<u>\$ 1,784</u>	<u>\$ 1,960</u>

## 7. Property and equipment

Property and equipment are as follows (in thousands):

	As of December 31,	
	2018	2017
Computer software and equipment	\$ 15	\$ 15
Office equipment and furniture	176	92
Laboratory equipment	1,571	1,529
Leasehold improvements	1,051	748
Construction in progress	—	22
Less accumulated depreciation	<u>(1,123)</u>	<u>(590)</u>
Property and equipment, net	<u>\$ 1,690</u>	<u>\$ 1,816</u>

Depreciation expense was \$0.5 million and \$0.4 million for the years ended December 31, 2018 and 2017, respectively.

## 8. Accrued expenses and other current liabilities

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

	As of December 31,	
	2018	2017
Employee-related expenses	\$ 2,043	\$ 1,435
Development costs and sponsored research	915	737
Clinical trials	607	69
Other	431	594
Total accrued expenses and other current liabilities	<u>\$ 3,996</u>	<u>\$ 2,835</u>

## 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. The Company provided the landlord with a security deposit in the form of a letter of credit in the amount of \$0.4 million which is recorded within both restricted cash and other assets in the Company's balance sheets as of December 31, 2018 and 2017.

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. The total estimated base rent payments over the term of the amended sublease approximate \$0.8 million.

Total rent expense, inclusive of lease incentives, under the operating lease agreements amounted to \$0.7 million and \$0.6 million for the years ended December 31, 2018 and 2017, respectively.

Aggregate future minimum annual rental commitments under these non-cancelable lease agreements are as follows at December 31, 2018 (in thousands):

<b>Year ending December 31,</b>	
2019	\$ 848
2020	860
2021	871
2022	587
2023	—
Thereafter	—
	<u>\$ 3,166</u>

## 10. Convertible preferred stock, tranche liability and stockholders' equity (deficit)

As described in Note 1, all previously outstanding convertible preferred stock was converted to common stock upon the completion of the Company's IPO in June 2018.

At December 31, 2017, convertible preferred stock consisted of the following (in thousands, except per share amounts):

	Shares authorized	Shares issued and outstanding	Issuance price per share	Carrying value	Liquidation preference
Series A-1	151,773	151,773	0.16472	\$ 22,650	\$ 25,000
Series A-2	173,453	173,453	0.23061	39,979	40,000
Series B	234,955	234,955	0.29793	69,757	70,000
Total	560,181	560,181		\$ 132,386	\$ 135,000

### *Series A preferred stock*

On May 4, 2016, the Company entered into a purchase agreement (the "Series A Purchase Agreement") for a private placement of up to 151,772,701 shares of Series A-1 Convertible Preferred Stock (the "Series A-1 Preferred Stock") and 173,453,018 shares of Series A-2 Convertible Preferred Stock (the "Series A-2 Preferred Stock" and together with the Series A-1 Preferred Stock, the "Series A Preferred Stock") under the Series A Purchase Agreement. Of the 325,225,719 authorized shares of Series A Preferred Stock, 151,772,701 shares were designated Series A-1 Preferred Stock at \$0.16472 per share and 173,453,018 shares were designated Series A-2 Preferred Stock at \$0.23061 per share. The Series A Purchase Agreement obligated the investors to purchase, at the election of the Company's board of directors (the "Board of Directors"), the Series A-2 Preferred Stock at \$0.23061 per share upon achieving certain clinical milestones. The determination as to whether the milestone event was met was subject to the certification by (i) the Board of Directors and (ii) the holders of at least a majority of the then-outstanding Series A Preferred Stock. The Series A Purchase Agreement also obligated the Company to sell to each investor that elects to purchase such investor's portion of Series A-2 Preferred Stock at any time such number of shares of Series A-2 Preferred Stock *pro rata* in accordance with the number of Series A-1 Preferred Stock purchased at the initial closing (the "Tranche Rights"). In January 2017, the Company achieved its clinical milestone obligating the Company to sell its Series A-2 Preferred Stock at \$0.23061 per share. The milestone closing occurred on February 2, 2017.

As of December 31, 2017, 151,772,701 shares of the Series A-1 Preferred Stock and 173,453,018 shares of the Series A-2 Preferred Stock were issued and outstanding. These shares were issued in exchange for cash proceeds of \$64.7 million, net of issuance costs.

### *Series B preferred stock*

On December 11, 2017, the Company entered into a purchase agreement (the "Series B Purchase Agreement") for a private placement of 234,954,520 shares of Series B Convertible Preferred Stock (the "Series B Preferred Stock"). All 234,954,520 authorized shares of Series B Preferred Stock were designated at \$0.29793 per share.

As of December 31, 2017, 234,954,520 shares of the Series B Preferred Stock were issued and outstanding. These shares were issued in exchange for cash proceeds of \$69.8 million, net of issuance costs.

### *Dividends*

The holders of the Series A and Series B Preferred Stock are not entitled to receive dividends unless declared by the Board of Directors of the Company in accordance with the Company's certificate of incorporation, as amended from time to time. No dividends have been declared since inception.

### *Liquidation preference*

Upon a liquidation of the Company, the assets of the Company or proceeds available for distribution to the Company's stockholders shall be paid as follows: (a) first, for each share of Series B Preferred Stock the greater of (i) one times the original purchase price plus declared and unpaid dividends on such share, or (ii) such amount as would have been payable had all shares of Series B Preferred Stock been converted to common stock immediately prior to such liquidation; and (b) then, for each share of Series A Preferred Stock the greater of (i) one times the original purchase price plus declared and unpaid dividends on such share, or (ii) such amount as would have been payable had all shares of (A) Series A-1 Preferred Stock been converted to common stock, in the case of Series A-1 Preferred Stock and (B) Series A-2 Preferred Stock been converted to common stock, in the case of Series A-2 Preferred Stock immediately prior to such liquidation. The balance of any proceeds shall be distributed pro rata to holders of common stock. If upon liquidation, the assets of the Company or proceeds available for distribution to its stockholders are insufficient to pay the holders of the Series B Preferred Stock as to their respective liquidation preferences the full amount entitled, the holders of the Series B Preferred Stock shall share ratably any distribution of the assets or proceeds available for distribution. If upon liquidation, the assets of the Company or proceeds available for distribution to its stockholders, after payment in full of the liquidation preferences to holders of the Series B Preferred Stock, are insufficient to pay the holders of the Series A Preferred Stock as to their respective liquidation preferences the full amount entitled, the holders of the Series A Preferred Stock shall share ratably any distribution of the remaining assets or proceeds available for distribution.

### *Conversion update*

Shares of preferred stock are convertible into such number of fully paid and non-assessable shares of common stock as determined by dividing the original issuance price by the conversion price at the time in effect, subject to adjustment. The original conversion price is \$0.16472 for Series A-1 Preferred Stock, \$0.23061 for Series A-2 Preferred Stock, and \$0.29793 for Series B Preferred Stock, in each case, subject to adjustments to reflect the issuance of common stock, options, warrants, or other rights to subscribe for or to purchase common stock for a consideration per share, less than the conversion price then in effect and subsequent stock dividends, stock splits, combinations, or recapitalizations.

Conversion is at the option of the respective holders of Series A and Series B Preferred Stock, although conversion is automatic upon the earlier of (a) the consummation of an underwritten public offering resulting in gross proceeds to the Company of at least \$70 million and a share price of at least \$0.446895 per share (subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization), or (b) the date and time, or the occurrence of an event, specified by the vote or written consent of the holders of at least majority of the then outstanding shares of Series A and Series B Preferred Stock, respectively; provided, that the outstanding shares of Series B Preferred Stock will not convert into shares of common stock pursuant to clause (b) without the approval of at least a majority of the then-outstanding Series B Preferred Stock, including one or more holders of Series B Preferred Stock that (i) individually, or together with such holders' affiliates, do not hold any Series A Preferred Stock and (ii) individually or collectively are the record holders of at least 30,208,439 shares of Series B Preferred Stock, subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization with respect to the Series B Preferred Stock.

### *Voting rights*

Holders of the Series A and Series B Preferred Stock are entitled to vote as a single class with the holders of common stock and shall have one vote for each equivalent common share into which the preferred stock is convertible. The holders of Series B Preferred Stock are entitled to elect one director to the Board of Directors; the holders of Series A Preferred Stock are entitled to elect four directors to the Board of Directors; and the holders of Preferred Stock and the holders of common stock on an as-converted to common stock basis, are entitled to elect the remaining directors.

### *Tranche rights with Series A preferred stock*

The Company concluded that the Tranche Rights met the definition of a freestanding financial instrument, as the Tranche Rights were legally detachable and separately exercisable from the Series A-1 Preferred Stock. Since the

Series A Preferred Stock was contingently redeemable upon the occurrence of a deemed liquidation event, the Tranche Rights are classified as an asset or liability under ASC 480, *Distinguishing Liabilities from Equity* and are initially recorded at fair value. The Tranche Rights were measured at fair value at each reporting period. Since the Tranche Rights were subject to fair value accounting, the Company allocated the proceeds to the Tranche Rights based on the fair value at the date of issuance with the remaining proceeds being allocated to the Series A-1 Preferred Stock.

The estimated fair value of the Tranche Rights was determined using a Monte Carlo simulation. The simulation considered the timing of achieving the successful clinical milestone, the post-money valuation as of May 2016, the risk-free rate commensurate with the estimated time until the Series A-2 transaction, and the volatility estimates.

Based on the analysis, the Company recorded a preferred stock tranche liability of \$2.1 million at the issue date to account for the obligation to issue shares of the Series A-2 Preferred Stock at a predetermined fixed price at the future settlement date. At December 31, 2016, the Company remeasured the fair value of the Tranche Rights and recognized a non-cash gain of \$2.1 million which was included in other income in the statements of operations and comprehensive loss. The milestone event obligating the Company to issue the Series A-2 Preferred Stock as of December 31, 2016 had been substantially achieved, and there was only a short amount of remaining time until the anticipated Series A-2 transaction. The Company concluded that the estimated fair value of the Series A-2 Preferred Stock was commensurate with the predetermined fixed price. As such, the preferred stock tranche liability had no value as of December 31, 2016. The milestone event occurred in January 2017, and the Company's Board of Directors and the holders of at least a majority of the then-outstanding Series A Preferred Stock certified that the milestone event had been achieved. The Series A-2 Preferred Stock was issued on February 2, 2017.

#### *Common stock*

As of December 31, 2018 and 2017, the Company had reserved common stock, on an as if converted basis, for issuance as follows (in thousands):

	<b>As of December 31,</b>	
	<b>2018</b>	<b>2017</b>
Series A-1 convertible preferred stock	-	5,502
Series A-2 convertible preferred stock	-	6,288
Series B convertible preferred stock	-	8,517
Stock options issued and outstanding	3,959	1,498
Unvested restricted stock	195	488
	4,154	22,293

## **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. The Company increased the number of shares reserved for issuance in the 2015 Plan in connection with each private placement of convertible preferred stock in May 2016, February 2017 and December 2017.

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, 2018 was 3,816,895, 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):

<b>Available for grant as of January 1, 2017</b>	496
Plan amendment	3,145
Grants	(1,226)
Forfeitures and cancellations	4
<b>Available for grant as of December 31, 2017</b>	2,419
Plan amendment	3,899
Grants	(2,515)
Forfeitures and cancellations	14
<b>Available for grant as of December 31, 2018</b>	3,817

*Stock-based compensation expense*

Non-cash stock-based compensation expense recognized in the accompanying statements of operations and comprehensive loss relating to both stock options and restricted stock awards for the years ended December 31, 2018 and 2017 are as follows (in thousands):

	Year ended December 31,	
	2018	2017
Research and development	\$ 866	\$ 325
General and administrative	2,452	576
<b>Total stock-based compensation expense</b>	<b>\$ 3,318</b>	<b>\$ 901</b>

*Restricted stock awards*

A summary of the status and changes of unvested restricted stock is presented below (in thousands, except per share amounts).

	Shares	Weighted- average grant date fair value per share
		\$
<b>Outstanding as of January 1, 2017</b>	781	\$ 1.10
Granted	—	—
Vested	(293)	\$ 1.10
Repurchased	—	—
Forfeited and canceled	—	—
<b>Outstanding as of December 31, 2017</b>	488	\$ 1.10
Granted	—	—
Vested	(293)	\$ 1.10
Repurchased	—	—
Forfeited and canceled	—	—
<b>Outstanding as of December 31, 2018</b>	195	\$ 1.10

In 2015, the Company granted 1.5 million restricted stock awards with a weighted-average grant date fair value per share of \$1.10. The restricted stock awards generally vest over four years, or a change in the control of the Company, subject to continued employment with the Company. In the event of a change in control, the unvested restricted stock awards will be accelerated and fully vested immediately prior to the change in control. There are no performance-based features or market conditions in the Company's outstanding restricted stock awards. The fair value of restricted stock awards is determined based on the number of restricted stock awards granted and the fair value of the Company's stock on the date of grant.

Non-cash restricted stock award expense recognized in the accompanying statements of operations and comprehensive loss was \$0.3 million for each of the years ended December 31, 2018 and 2017. The total fair value of shares that vested in 2018 was \$0.3 million. At December 31, 2018, there was \$0.2 million of unrecognized compensation cost related to unvested restricted stock awards that will be recognized as expense over a weighted-average period of 0.66 years.

*Stock options*

During the years ended December 31, 2018 and 2017, the Company granted 2.5 million and 1.2 million stock options, respectively. The options have a ten-year life and generally vest over a period of four years, subject to continuous employment. Once the options are exercised, the shares are subject to transfer restrictions under the terms of the Company's Stockholders' Agreement.

The weighted-average grant date fair value per share of each option granted during the years ended December 31, 2018 and 2017 was \$7.03 and \$1.66, respectively. As of December 31, 2018, there was \$16.4 million of total unrecognized stock-based compensation expense related to non-vested stock options which is expected to be recognized over a weighted-average period of 2.96 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, 2018 and 2017 were as follows:

	Year ended December 31,	
	2018	2017
Expected volatility	75%	75%
Expected dividends	None	None
Expected option life	6.08 Years	6.08 Years
Risk-free rate	2.81 – 3.06%	2.02 – 2.40%

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	Aggregat e intrinsic value
Outstanding, January 1, 2017	276	\$ 1.38	9.19	\$ 89
Granted	1,226	2.48		
Forfeited and canceled	(4)	1.93		
Outstanding, December 31, 2017	1,498	\$ 2.48	8.93	\$ 4,146
Granted	2,515	10.40		
Exercised	(40)	2.57		
Forfeited and canceled	(14)	4.79		
Outstanding, December 31, 2018	3,959	\$ 7.46	8.79	\$ 35,984
Vested and expected to vest at December 31, 2018	3,959	\$ 7.46	8.79	\$ 35,984
Exercisable at December 31, 2018	881	\$ 2.69	8.02	\$ 12,205

#### *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 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, 2018 and 2017 (in thousands, except per share data):

	Year ended December 31,	
	2018	2017
Numerator:		
Net loss attributable to common stockholders	\$ (53,281)	\$ (32,068)
Denominator:		
Weighted-average common shares outstanding—basic and diluted	20,199	5,196
Net loss per share attributable to common stockholders—basic and diluted	\$ (2.64)	\$ (6.17)

The following common stock equivalents outstanding as of December 31, 2018 and 2017, 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,	
	2018	2017
Series A-1 convertible preferred stock	—	5,502
Series A-2 convertible preferred stock	—	6,288
Series B convertible preferred stock	—	8,517
Stock options issued and outstanding	3,959	1,498
Unvested restricted stock	195	488
	4,154	22,293



### 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 \$0.2 million for the years ended December 31, 2018 and 2017, 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.

#### *Tax Cuts and Jobs Act*

With the enactment of the Tax Cuts and Jobs Act (“the Act”) on December 22, 2017, the Company’s 2017 financial results included a tax expense of \$6.1 million from remeasuring federal net deferred tax assets from 34% to 21%, which was fully offset by a valuation allowance. As of December 31, 2018, the Company has completed its accounting for all tax effects related to the Act, and there were no material adjustments recorded during the year to the provisional amounts reflected in the Company’s 2017 financial statements.

#### *Deferred tax assets and valuation allowance*

Deferred tax assets reflect the tax effects of net operating losses (“NOLs”), tax credit carryovers, 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, 2018, the Company had a U.S. federal NOL carryforward of \$97.3 million which is available to offset future taxable income. Of the \$97.3 million, \$48.9 million will begin to expire in 2035 and the remaining \$48.4 million has an indefinite carryforward period as a result of the Act. However, for NOLs arising after December 31, 2017, NOL carryforwards will be limited to 80% of taxable income. As of December 31, 2018, the Company had state NOL carryforwards of \$9.2 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:

<b>Year ended December 31,</b>	<b>2018</b>	<b>2017</b>
Federal rate	21.0 %	34.0 %
State rate	7.5	5.7
Effects of the Tax Cuts and Jobs Act	—	(18.9)
Valuation allowance	(26.8)	(18.8)
Provision to return	(0.0)	(2.6)
Other	(1.7)	0.6
	—%	—%

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

December 31,	2018	2017
Deferred tax assets		
Net operating loss	\$ 27,749	\$ 13,920
Accrued clinical trials	322	82
Accrued compensation	582	409
Accrued expenses and other, net	374	456
Total deferred tax assets	29,027	14,867
Less valuation allowance	(28,963)	(14,688)
Net deferred tax assets	64	179
Deferred tax liabilities		
Stock-based compensation and other, net	(64)	(179)
Net deferred taxes	\$ —	\$ —

Pursuant to Section 382 of the Internal Revenue Code, certain substantial changes in the Company's ownership may result in a limitation on the amount of NOL carryforwards and tax carryforwards that may be used in future years. Utilization of the NOL and tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 ("IRC Section 382") due to ownership change limitations that have occurred previously or that could occur in the future. These ownership changes may limit the amount of NOL and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. During 2018, the Company performed a detailed analysis of their historical and current IRC Section 382 ownership changes that may limit the utilization of NOL carryforwards. Except for approximately \$7.1 million of NOLs arising prior to the Company's Series A preferred stock financing in May 2016, the entire remaining NOL carryforward is available for immediate use based on the IRC Section 382 analysis performed. There could also be additional ownership changes in the future which may result in limitations on the utilization of NOL carryforwards and credits.

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, 2018, the Company's tax years through December 31, 2017 are subject to examination by the U.S. federal and state taxing authorities.

## 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, 2018.

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, 2018. The Company does not anticipate recognizing any significant losses relating to these arrangements.

## 16. Subsequent events

### *Grant of stock options under the 2018 Plan*

In January 2019, the Company granted options for the purchase of 1.0 million shares of common stock at a weighted-average exercise price of \$19.33 per share.

**Item 16. Form 10-K Summary**

The Company has elected not to include summary information.

## EXHIBIT INDEX

<u>Exhibit No.</u>	<u>Exhibit Index</u>
3.1	Amended and Restated Certificate of Incorporation of the Registrant, 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).
3.2	Amended and Restated Bylaws of the Registrant, 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).
4.1	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).
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, 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).
10.6#	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., President and 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, 2018, 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 (v) Notes to Financial Statements.

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† 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.

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NASDAQ: APTX

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