TorreyPines Therapeutics, Inc.
Form 10-K
March 31, 2008

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2007

Or

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

For the transition period from to
Commission File Number: 000-25571

TorreyPines Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

DELAWARE	**86-0883978**
State or other jurisdiction of incorporation or organization	(I.R.S. Employer Identification No.)
11085 North Torrey Pines Road, Suite 300 La Jolla, California	**92037**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(858) 623-5665**

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

Common Stock, $0.001 par value
(Title of class)

The Nasdaq Stock Market LLC
(Name of Each Exchange on Which Registered)

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 o No ý

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

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 ý No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 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. ý

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of "accelerated filer," "large accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company ý

Indicate by check mark where the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes o No ý

The aggregate market value of the Common Stock of the registrant (the "Common Stock") held by non-affiliates of the registrant, based on the last sale price of the Common Stock on June 29, 2007 (the last business day of the registrant's most recently completed second fiscal quarter) of $6.95 per share as reported by the Nasdaq Global Market, was approximately $67,306,000. Shares of Common Stock held by each officer and director and by each person who is known by the registrant to own 5% or more of the outstanding Common Stock, if any, have been excluded in that such persons may be deemed to be affiliates of the registrant. Share ownership information of certain persons known by the registrant to own greater than 5% of the outstanding common stock for purposes of the preceding calculation is based solely on information on Schedules 13D and 13G, if any, filed with the Securities and Exchange Commission and is as of June 29, 2007. This determination of affiliate status is not necessarily a conclusive determination for any other purposes.

As of March 14, 2008 there were 15,745,127 shares of our Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement to be filed with the Securities and Exchange Commission by April 29, 2008 are incorporated by reference into Part III of this Annual Report on Form 10-K.

TORREYPINES THERAPEUTICS, INC.
FORM 10-K

For the Year Ended December 31, 2007

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PART I

Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements that involve a high degree of risk and uncertainty. Such statements include, but are not limited to, statements containing the words "believes," "anticipates," "expects," "estimates" and words of similar import. Our actual results could differ materially from any forward-looking statements, which reflect management's opinions only as of the date of this report, as a result of risks and uncertainties that exist in our operations, development efforts and business environment. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should carefully review the risks described in "Risk Factors" and elsewhere in this Annual Report on Form 10-K and the risk factors described in other documents that we file from time to time with the Securities and Exchange Commission, or SEC, including our Quarterly Reports on Form 10-Q.

TorreyPines Therapeutics and design, our tree logo and Posiphen are our trademarks or registered trademarks in the United States and certain other countries. We may also refer to trademarks of other corporations and organizations in this document.

Item 1. Business.

Overview

All references to "TorreyPines," "we," "us," "our" or the "Company" mean TorreyPines Therapeutics, Inc. and its subsidiaries, except where it is made clear that the term means only the parent company.

We are a biopharmaceutical company committed to providing patients with better alternatives to existing therapies through the research, development and commercialization of small molecule compounds. Our goal is to develop versatile product candidates each capable of treating a number of acute and chronic diseases and disorders such as migraine, chronic pain, muscle spasticity and rigidity, xerostomia and cognitive disorders. We are currently developing four product candidates, two ionotropic glutamate receptor antagonists and two muscarinic receptor agonists.

Our two ionotropic glutamate receptor antagonists, tezampanel and NGX426, are currently in clinical development. Tezampanel and NGX426 competitively block the binding of glutamate at the AMPA and kainate receptor subtypes. While normal glutamate is essential, excess glutamate has been implicated in a number of diseases and disorders. Tezampanel and NGX426 are the first glutamate receptor antagonists with this combined binding activity to be tested in humans. In October 2007 we released the results of a Phase IIb clinical trial of tezampanel, our most advanced product candidate. In this clinical trial, a single dose of tezampanel given by injection was statistically significant compared to placebo in treating acute migraine headache. This was the sixth Phase II trial in which tezampanel has been shown to have analgesic activity. We intend to hold an end of Phase II meeting with the United States Food and Drug Administration, or FDA, in the second half of 2008 to discuss the scope of a Phase III program for tezampanel in acute migraine. Assuming a successful outcome of this meeting, and additional financial resources, we plan to move forward with a Phase III program with tezampanel for the treatment of acute migraine. Also, in the second half of 2008 we plan to initiate a small, Phase II trial of tezampanel for the treatment of muscle spasticity and rigidity, a disorder commonly associated with spinal cord trauma, stroke, and multiple sclerosis. If initiated, this will be our first clinical trial of tezampanel in a non-pain indication.

NGX426 is an oral prodrug of tezampanel. In clinical trials, NGX426 has been shown to rapidly convert to tezampanel. We intend to complete our on-going Phase I maximum tolerated single dose

clinical trial of NGX426 in the first half of 2008. Once this study is completed and the maximum tolerated dose has been identified, we intend to initiate a Phase I trial to evaluate multiple doses of NGX426 given to healthy adults. Also in the first half of 2008, we plan to initiate a clinical trial in healthy adults to determine the analgesic effect of NGX426.

Our muscarinic receptor agonist currently in clinical development is NGX267. We have completed three Phase I clinical trials evaluating single and multiple doses of NGX267 given to healthy adults. In March 2008, we initiated a Phase II clinical trial in patients to evaluate NGX267 for the treatment of xerostomia, or dry mouth, secondary to Sjogren's syndrome. Additionally, based on its mechanism of action, we believe NGX267 may also be developed to treat cognitive disorders such as Alzheimer's disease and cognitive impairment associated with schizophrenia, or CIAS. However, we have no plans to initiate any clinical trials of NGX267 in Alzheimer's disease or CIAS in 2008. NGX292, our other muscarinic receptor agonist, is structurally similar to NGX267 and is in preclinical development.

We also have two drug discovery programs, a gamma-secretase modulator, or GSM, program and an Alzheimer's disease genetics program. These programs are focused on discovering and validating novel small molecule compounds and molecular targets for Alzheimer's disease. Our genetics program is undertaken in collaboration with Eisai Co., Ltd., or Eisai.

In 2008 we will evaluate partnership opportunities for tezampanel, NGX426 and NGX267 to enable us to pursue the numerous commercial opportunities we have identified for these product candidates. This will be in addition to our on-going partnering activities involving our GSM program.

Our Clinical Development Opportunities

In 2008, the goal of our clinical development plan is to demonstrate the therapeutic versatility of tezampanel, NGX426 and NGX267. The following chart presents these three product candidates, select development opportunities, and current clinical status:

Product Candidate	Development Opportunity	Clinical Status
Ionotropic Glutamate Antagonists		
Tezampanel	Migraine	Phase IIb
Tezampanel	Muscle Spasticity and Rigidity	Phase I
NGX426	Migraine	Phase I
NGX426	Neuropathic Pain	Phase I
Muscarinic Receptor Agonists		
NGX267	Xerostomia	Phase II
NGX267	Alzheimer's disease	Phase I
NGX267	CIAS	Phase I

We currently have worldwide commercial rights to all of our product candidates in clinical development.

Tezampanel and NGX426 Ionotropic Glutamate Receptor Antagonists, AMPA and Kainate Subtype

We in-licensed tezampanel and NGX426 from Eli Lilly & Company, or Eli Lilly, in 2003. Based on their mechanism of action as well as preclinical and clinical data, we believe these first-in-class product candidates have the potential to be effective across numerous indications in a wide range of therapeutic areas.

Mechanism of Action

Tezampanel and NGX426 are ionotropic glutamate receptor antagonists. These product candidates act as competitive antagonists of the AMPA and kainate subtype of ionotropic glutamate receptors.

Glutamate receptors mediate the functioning of glutamate, an important excitatory neurotransmitter. While normal glutamate production is essential, excess glutamate production, either through injury or disease, can have a range of pathological effects. By acting at both the AMPA and kainate receptor site to competitively block the binding of glutamate, both tezampanel and NGX426 have the potential to treat a number of diseases and disorders. These include chronic pain, such as migraine and neuropathic pain, muscle spasticity and rigidity, thrombosis, epilepsy, Parkinson's disease and a condition known as central sensitization, a persistent state of hypersensitivity to pain that is a core component of many pain conditions. In addition to the clinical data we have generated for tezampanel and NGX426 in migraine and neuropathic pain, these potential indications are supported by either preclinical data or scientific literature.

Migraine

Migraine is a chronic, intermittent pain condition often accompanied by central sensitization. The 2005 American Migraine Prevalence and Prevention study, sponsored by the National Headache Foundation, estimated that there are approximately 30 million people who suffer from migraines in the United States, with fewer than half that number seeking treatment. This study also confirmed that a large number of migraine sufferers are not getting adequate treatment or the relief they need, despite the number of products available to treat migraines. It has been more than a decade since the FDA has approved a migraine treatment with a new mechanism of action.

The medications most commonly used to treat acute migraine are triptans and ergotamines. These drugs constrict or narrow the blood vessels in the brain, heart and periphery. When the blood vessels in the brain are constricted, the blood flow is decreased thus relieving the throbbing pain associated with migraine.

An emerging theory is that the brain itself, not just the blood vessels, may cause or contribute to the migraine. Published data show that during a migraine, increased levels of glutamate activate AMPA and kainate receptors, resulting in the transmission of pain and, in many patients, the development of central sensitization. Tezampanel has been shown in preclinical studies to block the binding of glutamate to these receptors. In doing so, tezampanel relieves the migraine pain and may prevent or lessen the development of central sensitization without directly constricting the blood vessels. As a result, tezampanel may offer a significant safety advantage over drugs such as the triptans and ergotamines for patients with cardiovascular risk factors.

Migraine is often accompanied by central sensitization, which is characterized by allodynia and hyperalgesia. Allodynia is a painful response to a normally non-painful stimulus such as touch, sound, temperature, or light. Hyperalgesia is an exaggerated sensitivity to a normally painful stimulus. Recent data suggest that the triptans do not work as well in migraine patients who present with symptoms of central sensitization. In contrast, preclinical data show that tezampanel's analgesic activity is especially pronounced in the presence of central sensitization. Because of its positive effects in treating central sensitization, tezampanel may have an important role to play not only in treating the acute migraine pain, but also in preventing migraines by addressing the underlying cause.

Neuropathic Pain

Neuropathic pain is a complex, chronic pain condition in which the peripheral or central nervous system itself is damaged, dysfunctional or injured. The malfunctioning nerves become the cause of the pain, sending incorrect signals to pain centers. Because it is often difficult to recognize and determine the cause of the neuropathic pain, it is often under-treated. Some common causes of neuropathic pain include spinal or back injury or surgery, diabetes, HIV infection and herpes. A hallmark of neuropathic pain is central sensitization. The signs and symptoms of central sensitization in patients with neuropathic pain are similar to those in patients with migraine, namely allodynia and hyperalgesia. In a

Phase II trial, tezampanel, given intravenously, was shown to relieve neuropathic pain and reduce the signs and symptoms of central sensitization.

Muscle Spasticity and Rigidity

Muscle spasticity and rigidity is a motor system disorder that results in an abnormal and painful increase in muscle contraction, or spasticity, and muscle tone, or rigidity. Spasticity and rigidity are usually caused by damage to the portion of the brain or spinal cord that controls voluntary movement and may occur in association with spinal cord injury, multiple sclerosis, cerebral palsy, brain damage, severe head injury, Parkinson's disease or other progressive motor system disorders. In a preclinical study in rats, tezampanel was shown to reduce both muscle spasticity and rigidity without any significant side effects.

Clinical Development Overview Tezampanel

Using intravenous administration of tezampanel, proof of concept clinical testing has been successfully completed in migraine, low back pain, neuropathic pain via a capsaicin model, post-operative dental pain and pain from spinal cord trauma. In order to evaluate tezampanel given by injection, we completed a Phase I clinical trial and determined that a single dose of tezampanel given by injection was well tolerated at all doses up to and including 100 mg. To date tezampanel has been shown to be safe and well-tolerated in three Phase I and six Phase II clinical trials involving more than 450 patients and healthy adults.

In October 2007, we released results of a Phase IIb clinical trial of tezampanel, given by injection, in patients who suffer a single acute migraine attack. The clinical trial was a randomized, double-blind, placebo-controlled, parallel-group, single dose study to evaluate three doses of tezampanel, 40 mg, 70 mg, and 100 mg, compared to placebo. A total of 306 patients were enrolled in the trial, with approximately 75 subjects per treatment arm. This clinical trial demonstrated that the 40 mg dose of tezampanel demonstrated statistically significant improvement on headache pain response, the primary endpoint, at two hours post-dose compared to placebo. Two other doses of tezampanel, 70 mg and 100 mg, were evaluated and also demonstrated effects across a number of pain measurements although neither dose reached statistical significance on the primary endpoint. Although not powered to demonstrate statistical significance, improvement in key secondary measures at 40 mg were either statistically significant or trending when compared to placebo and corroborated the results for the primary endpoint of the study. In this trial, all three doses of tezampanel were well-tolerated. There were no serious or medically important adverse events reported. The most common adverse events associated with all doses of tezampanel, as well as placebo, were dry mouth, somnolence, dizziness, injection site burning and injection site pain. Injection site burning and injection site pain were more frequently reported in the placebo group. For tezampanel, the overall incidence of reported adverse events was dose related with the lowest incidence at the 40 mg dose.

In February 2008 we released results of a multiple dose clinical trial of tezampanel, given by injection. The Phase I double-blind, placebo-controlled trial enrolled 30 normal healthy male and female adults. The data from this trial show that tezampanel given by injection once-daily for four consecutive days at doses of 40 mg, 70 mg and 100 mg was safe and well-tolerated. There were no discontinuations from the study and reported adverse events were generally mild and transient. These Phase I results support our continued development of tezampanel across a variety of chronic conditions.

We intend to hold an end of Phase II meeting with the FDA in the second half of 2008 to discuss the scope of a Phase III program for tezampanel in acute migraine. Assuming a successful outcome of this meeting, and additional financial resources, we plan to move forward with a Phase III program with tezampanel for the treatment of acute migraine. In addition, in the second half of 2008 we intend

to initiate a Phase II clinical trial of tezampanel in muscle spasticity and rigidity, which will be our first non-pain indication evaluated in the clinic.

Clinical Development Overview NGX426

The results of our first Phase I single dose clinical trial of NGX426, given orally, demonstrated that NGX426 was well-tolerated and rapidly converted to tezampanel at 10 mg, 20 mg, and 30 mg. In our on-going second Phase I clinical trial we intend to identify the maximum tolerated single dose of NGX426 when given to healthy adults. This clinical trial is designed as a randomized, double-blind, placebo-controlled study in which healthy adults will receive placebo or an escalating single dose of NGX426. We have completed dosing of subjects up to 150 mg and we will continue to dose until we reach either the maximum tolerated dose or up to a maximum of 210 mg. We expect to report results of this clinical trial in the second half of 2008.

In the first half of 2008 we plan to evaluate the analgesic effect of NGX426 in healthy adults. The purpose of this trial is to show that tezampanel, when given orally as NGX426, maintains its analgesic activity. Additionally, in the second half of 2008 we intend to initiate a Phase I multiple dose trial of NGX426 in healthy adults.

NGX267 and NGX292 Muscarinic Receptor Agonists

We in-licensed NGX267 and NGX292 from Life Science Research Israel, or LSRI, in 2004. NGX267 is currently in Phase II clinical development for xerostomia secondary to Sjogren's syndrome. NGX292 is structurally similar to NGX267 and is currently in preclinical testing.

Mechanism of Action

There is extensive data validating the rationale for using muscarinic receptor agonists in the symptomatic treatment of cognitive impairment. This rationale, based on the cholinergic hypothesis of learning and memory, links disturbances in acetylcholine function with changes in cognition. Many of the currently approved treatments for symptomatic improvement of Alzheimer's disease are based on this cholinergic hypothesis. NGX267, a partial muscarinic receptor agonist with functionally specific M1 receptor activity, mimics the action of acetylcholine by stimulating the M1 receptors. In animal models NGX267 has been shown to be effective in improving cognitive deficits in learning and memory.

In addition to improving cognition, a second mechanism of action, the reduction of $A\beta_{42}$, also supported by preclinical data, suggests that NGX267 may be effective as a treatment to delay the onset or to slow the progression of Alzheimer's disease. It has also long been hypothesized that the cause of Alzheimer's disease lies in the build up of protein deposits, referred to as amyloid plaques, in the brain. The plaques are largely comprised of aggregations of a peptide referred to as amyloid ß, or Aß, peptide. A specific Aß peptide, $A\beta_{42}$, is thought to play a significant role in the cause of Alzheimer's disease. In transgenic mice, a specific testing model where the animals have characteristics of Alzheimer's disease, NGX267 has been shown to reduce $A\beta_{42}$ and to prevent the formation of amyloid plaques. NGX292 has demonstrated a biological profile similar to the profile of NGX267.

Xerostomia

Xerostomia, or dry mouth, may be caused by an underlying disease such as Sjogren's syndrome or may also result from medical treatments such as radiation therapy to the head or neck. In evaluating NGX267 as a treatment for xerostomia, we are leveraging a known biological effect of muscarinic receptor agonists. Similar to acetylcholine, when muscarinic agonists stimulate the M1 receptor, they produce cholinergically-mediated side effects such as salivation, sweating, and tearing. In two Phase I trials, NGX267 has been shown to stimulate the M1 receptor and, depending on dose, produce these side effects. We believe that we have identified a therapeutic dose range for NGX267 that will alleviate

complaints of dry mouth without producing unpleasant or intolerable side effects such as excessive sweating. There are currently only two prescription medications for the treatment of xerostomia. Both of these medications have side effects and may not be suitable for all sufferers of dry mouth.

Alzheimer's Disease and CIAS

There are currently no approved products to treat the underlying cause of Alzheimer's disease or to modify the progression of the disease. All of the approved products, as well as many of the compounds under development for Alzheimer's disease, treat or intend to treat only the signs and symptoms of Alzheimer's disease. With regard to CIAS, an emerging approach to improving the functional ability of patients with schizophrenia is to develop therapies that will improve their cognitive impairment. There are no current approved therapies for CIAS. Because impairments in memory and learning have been demonstrated in both Alzheimer's disease patients and schizophrenic patients, we believe that there is a strong rationale to develop NGX267 as a treatment for Alzheimer's disease as well as CIAS.

Clinical Development Status

We have completed three Phase I clinical trials of NGX267. In the first trial, we identified the maximum tolerated single dose of NGX267 as 35 mg in healthy young adult males. All doses up to and including 35 mg were well tolerated by the subjects and there were no reports of clinically significant adverse events. In the second trial, we confirmed the safety and tolerability of a single dose of NGX267 up to 15 mg in a healthy elderly population. In addition, at 15mg, statistically significant increases in salivary flow were demonstrated for NGX267 in comparison to placebo in the study.

We have also completed a multiple dose Phase I clinical trial of NGX267 in healthy adult males. Subjects received either a 10, 20 30 or 35 mg dose of NGX267 once-daily for each of four consecutive days. NGX267 was safe and well tolerated in the trial with no clinically significant adverse events. In the study, statistically significant increases in peak and total salivary flow were demonstrated for NGX267 in comparison to placebo and these effects were maintained over four days of dosing.

In March 2008 we initiated a Phase II clinical trial of NGX267 in patients suffering from xerostomia secondary to Sjogren's syndrome. The clinical trial is a randomized, double-blind, placebo-controlled design and will enroll 24 patients. Using a cross-over design, each patient will receive a once-daily oral dose of placebo, 10 mg, 15 mg and 20 mg of NGX267 in four distinct treatment periods. We have no plans to initiate any clinical trials of NGX267 in Alzheimer's disease or CIAS in 2008.

Our Drug Discovery Programs

We have two drug discovery programs, a gamma-secretase modulator program and an Alzheimer's disease genetics program. These programs are focused on discovering and validating novel small molecule compounds and molecular targets for Alzheimer's disease. Our genetics program is undertaken in collaboration with Eisai.

Gamma-secretase Modulator Program

Our approach to Alzheimer's disease drug discovery is firmly rooted in the amyloid hypothesis. First generation approaches to lowering $A\beta_{42}$ focused on inhibiting, as opposed to modulating, the activity of a large, complex and essential enzyme called gamma-secretase that is involved in the production of $A\beta_{42}$. Gamma-secretase inhibitors have been associated with side effects presumably because they completely block the functioning of the enzyme towards other biologically important substrates.

We have identified two distinct series of second generation compounds that modulate the gamma-secretase enzyme as opposed to inhibiting it. These gamma-secretase modulators, or GSMs, reduce the brain levels of $Aß_{42}$ while maintaining the overall balance of Aß in the brain. They do this by influencing the enzyme to make shorter, less toxic Aß peptides at the expense of the longer, toxic $Aß_{42}$ peptide. Because GSM compounds allow the gamma-secretase enzyme to perform its normal functions on other substrates, it is believed they will likely not have some of the side effects associated with the first generation compounds that fully inhibited enzyme function.

Our GSM compounds are small molecules that have been shown to penetrate the blood brain barrier upon chronic oral dosing in rodents. We believe that in the brain, they preferentially lower $Aß_{42}$ levels by modulation of gamma-secretase.

Alzheimer's Disease Genetics Program

Since its inception in 2001, our Alzheimer's disease genetics program has been a shared research effort between us and Eisai. Our genetics research program integrates human genetic mapping, genomics, and bioinformatics. The goals of our genetics research program are two-fold: to provide new targets for drug discovery, and to facilitate methods for reliably predicting and diagnosing Alzheimer's disease.

Recent data suggests that up to 80% of cases of Alzheimer's disease have a genetic component. In 2005, the scope of our Alzheimer's disease genetics program was significantly expanded to include a comprehensive and state-of-the-art screening of over 400 families, comprising more than 1,600 participants with late-onset Alzheimer's disease. The resulting whole-genome family-based association screen is expected to identify up to 95% of the genetic variants and mutations conferring risk or protection for Alzheimer's disease. Once completed, this screening may enhance our ability to identify novel pathways involved in the cause and course of Alzheimer's disease and to strengthen our pipeline with new targets for drug discovery.

Strategic Alliance, License and Other Commercial Agreements

Drug development is long and costly and we recognize that we will need strategic partners to maximize the potential of one or more of our product candidates. Our goal is to strike a balance between advancing product development at our expense and partnering with third parties at key points along the development path. Overall, our strategy is to reach key milestones with our product candidates before entering into strategic alliances. We believe that, in this way, we can retain significant commercial value in the product candidates while obtaining strategic and financial assistance to advance our programs. We speak to prospective partners on a regular basis, understanding that discussions and ultimately mutually beneficial strategic alliances are the result of developing on-going relationships. In 2008 we will evaluate partnership opportunities for tezampanel, NGX426 and NGX267 to enable us to pursue the numerous commercial opportunities we have identified for these product candidates. This will be in addition to our on-going partnering activities involving our GSM program.

In addition to strategic development alliances, our alliance strategy also includes entering into agreements or partnerships that provide pharmaceutical drug developers with access to our drug discovery technologies. We currently have one such strategic alliance with Eisai for our Alzheimer's disease genetics research program.

Since inception, our revenue has been derived from our strategic alliances. For the fiscal year ended December 31, 2007, 100% of our revenue was derived from our agreements with Eisai.

Eisai

Since 2001, we have had an on-going relationship with Eisai with respect to our Alzheimer's disease drug and target discovery programs. In October 2005, we entered into a cooperation agreement with Eisai to continue to work together on our Alzheimer's disease genetics research program that focuses on the discovery of genes responsible for late onset Alzheimer's disease. The agreement had an initial two-year term that Eisai extended for an additional 12 months. This agreement will conclude on October 1, 2008. Under the agreement, Eisai is funding our work regarding the genetics program and Eisai has exclusive time-limited rights of first negotiation and refusal for gene targets discovered and validated in the course of the genetics program. The total payments we may receive under this agreement are approximately $15.0 million, which includes research support and a cash payment for the right of first negotiation and refusal. As of March 15, 2008 we have received approximately $13.0 million from Eisai pursuant to this agreement. We also had a collaboration agreement with Eisai regarding our GSM program that expired on February 29, 2008.

Eli Lilly

In 2003, we entered into a development and licensing agreement with Eli Lilly to obtain an exclusive license to Eli Lilly's ionotropic glutamate receptor antagonist asset tezampanel, and its prodrug NGX426. We paid Eli Lilly an up-front license fee of $6.0 million under the agreement. If specified development, regulatory and commercial milestones are achieved, we are obligated to make milestone payments to Eli Lilly. We are also obligated to pay royalties to Eli Lilly on any sales of tezampanel and NGX426. We are required to use commercially reasonable efforts to develop and commercialize the product candidates subject to the agreement, including use of commercially reasonable efforts to achieve specified development events within specified timeframes.

The term of the development and licensing agreement will continue until all royalty payment obligations have expired on a country-by-country basis, unless the agreement is earlier terminated. Under certain termination circumstances, all of the rights granted to us under the agreement will revert to Eli Lilly.

Life Science Research Israel (LSRI)

In 2004, we entered into an agreement with LSRI to obtain an exclusive license to their muscarinic receptor agonist assets NGX267 and NGX292. No up-front license fee was paid. For the first two years of the agreement, we provided specified amounts of research funding to LSRI. Through December 31, 2007 we paid LSRI total milestone payments of approximately $2.2 million. If additional specified development, regulatory and commercial milestones are achieved, we are obligated to make milestone payments to LSRI which may total up to an additional $18.3 million. We are also obligated to pay royalties to LSRI on sales of NGX267 and NGX292 and to pay LSRI a percentage of specified payments we receive upon sublicensing rights to either compound, subject to a minimum amount payable to LSRI for the first sublicense. If we sublicense rights to a compound after a specified point in development of the compound, LSRI will select the level of royalty and sublicense payments from among the alternatives provided in the agreement. We are required to use commercially reasonable efforts to develop and commercialize the product candidates subject to the agreement, including use of commercially reasonable efforts to achieve specified development events within specified timeframes.

The term of the agreement will continue on a country-by-country basis until the later of a specified number of years from the date of first commercial sale of a product in such country or the expiration in such country of the last-to-expire patent covering a product candidate licensed under the agreement, provided, however, that in the event that generic competition occurs in such country and results in a loss of a certain percentage of the market share for such product then the royalty payments will terminate in such country.

University of Iowa Research Foundation

We have a license agreement with the University of Iowa Research Foundation, or UIRF, pursuant to which UIRF has granted us an exclusive United States license to certain patents and patent applications relating to spinal administration of tezampanel. Under the terms of the agreement we have the right to sublicense our license.

If we achieve specified regulatory and patent-related milestones, we will be obligated to make milestone payments to UIRF which may total up to $0.4 million. We must also pay UIRF an annual license maintenance fee which may be reduced by the amount of other payments made by us to UIRF under the agreement. We are also obligated to pay royalties to UIRF on any sales of tezampanel using the licensed patent rights and to pay UIRF a percentage of specified payments we receive upon sublicensing rights to the licensed patent rights. We are required to use commercially reasonable efforts to commercialize products using the licensed patent rights.

This agreement will continue until the expiration of the last-to-expire of the licensed patents and patent applications unless earlier terminated.

Johnson & Johnson Development Corporation

On March 24, 2008, we entered into a mutual agreement with Johnson & Johnson Development Corporation, or JJDC, terminating the letter agreement between the parties dated August 26, 2004 that granted JJDC an exclusive right of first negotiation with us regarding rights or products related to our M1 agonist program. As a result of the termination of the original agreement, the rights and obligations of the parties, including but not limited to the right of first negotiation granted to JJDC by us with respect to rights or products related to our M1 agonist program have terminated.

Competition

We and our strategic alliance partners face intense competition. We are in competition with fully integrated pharmaceutical companies, smaller companies that may be collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors have prescription products for chronic pain, such as migraine and neuropathic pain, muscle spasticity and rigidity, xerostomia and Alzheimer's disease already approved by the FDA or they are pursuing the same or similar approaches to those which constitute our discovery and development platforms and operate larger discovery and development programs in these fields than ours. We believe that competition for the migraine, neuropathic pain, muscle spasticity and rigidity, xerostomia and Alzheimer's disease products that we and any future strategic alliance partners may develop will come from companies that are conducting research, engaging in clinical development, or currently marketing and selling therapeutics to treat these conditions. These competitors include the pharmaceutical industry's leading companies.

For example, triptans are the most commonly prescribed drugs for the treatment of moderate to severe migraine. There are seven triptans approved for use and Imitrex®, marketed by GlaxoSmithKline, dominates the market. Other triptans are: Zomig®, Maxalt®, Amerge®, Frova , Axert®, and Relpax®. According to PhRMA's 2006 report, *Medicines in Development for Neurologic Disorders,* there are more than 30 companies seeking to develop compounds to treat migraine and pain disorders or to obtain additional indications to broaden the use of currently approved pain relieving prescription medications. This list includes most of the large pharmaceutical companies such as Abbott Laboratories, AstraZeneca, Eisai, Elan, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, and Wyeth Pharmaceuticals as well as small and mid-sized biotechnology companies.

There are a variety of approaches to treating muscle spasticity and rigidity including physical therapy, medications and surgery. The most commonly prescribed medications are oral muscle relaxants

such as Lioresal® (Novartis), Dantrium® (Procter and Gamble), Zanaflex® (Acorda) and Valium® (Roche). Often a combination of these medications may be prescribed to achieve control of spasticity. While effective, some of these medications can cause drowsiness which may limit their use in some patients. In addition, there has been some recent clinical studies showing that gabapentin, a drug used to treat neuropathic pain, and Botox® (Allergan) may be effective in treating spastic muscles.

In the neuropathic pain market, we would compete with companies such as Pfizer, marketing Neurontin and Lyrica®, and Eli Lilly, marketing Cymbalta® in addition to opiods approved for treating neuropathic pain, off-label uses of products to treat neuropathic pain and generics products. Given the size of the neuropathic pain market, approximately $3.5 billion in 2006 and expected to double by 2016, it is likely that most of the large pharmaceutical companies as well as many biotechnology companies will look to develop compounds to treat neuropathic pain.

In the xerostomia market, Salagen®, marketed by MGI Pharma, and Evoxac®, marketed by Daiichi Pharmaceutical Corporation, are the only two prescription medications available to treat xerostomia. Each of these compounds are muscarinic receptor agonists. In addition, there are many over the counter medications that are used to treat dry mouth.

Despite limited effectiveness, acetylcholinesterase inhibitors are the mainstay treatment option for Alzheimer's disease. Four acetylcholinesterase inhibitors are approved for the symptomatic improvement of mild to moderate Alzheimer's disease: Aricept, the market leader, Exelon, Razadyne (formally Reminyl), and Cognex. One additional product, Namenda, a compound with a different mechanism of action, is approved for symptomatic improvement in patients with moderate to severe Alzheimer's disease. According to PhRMA's 2006 report, *Medicines in Development for Neurologic Disorders,* there are more than 25 companies, among others, seeking to develop compounds to treat Alzheimer's disease or to obtain additional indications to broaden the use of currently approved treatments for Alzheimer's disease. This list includes most of the large pharmaceutical companies such as Abbott Laboratories, AstraZeneca, Eisai, Elan, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, and Wyeth Pharmaceuticals as well as small and mid-sized biotechnology companies.

There are no FDA approved drugs for the treatment of CIAS. Through various market reports and company announcements, we believe that there are more than 20 companies seeking to develop compounds to treat cognitive disorders in general, often without any specific reference to CIAS. This list includes most of the large pharmaceutical companies such as Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Novartis, and Roche as well as small and mid-sized biotechnology companies.

Many of our competitors, either alone or together with their collaborative partners, have substantially greater financial resources than us, as well as greater experience in developing pharmaceutical products, undertaking preclinical testing and human clinical trials, obtaining FDA and other regulatory approvals of products, formulating and manufacturing pharmaceutical products, and launching, marketing, distributing and selling products.

Proprietary Rights

Patent Applications

Our policy is to pursue patents, both those generated internally and those licensed from third parties, pursue trademarks, maintain trade secrets and use other means to protect our technology, inventions and improvements that are commercially important to the development of our business.

Our success will depend significantly on our ability to:

- obtain and maintain patent and other proprietary protection for the technology, inventions and improvements we consider important to our business;
- defend our patents;

preserve the confidentiality of our trade secrets; and

operate without infringing the patents and proprietary rights of third parties.

As of December 31, 2007, we controlled approximately 279 patents and patent applications worldwide. Of these, 55 pertain to tezampanel and/or NGX426 (including 13 issued U.S. patents), 53 pertain to NGX267 and/or NGX292 (including 3 issued U.S. patents), 76 pertain to phenserine and/or Posiphen (including 3 issued U.S. patents), 40 pertain to bisnorcymserine (including 2 issued U.S. patents), and 19 pertain to our GSM program (including 1 issued U.S. patent). Issued patents, and patents that may issue from these pending applications, would expire between 2010 and 2028. In accordance with the Hatch-Waxman Act in the United States, and corresponding legislation in certain foreign countries, patents covering our drug products may be eligible for up to five years of patent term restoration.

Trademarks, Trade Secrets and Other Proprietary Information

We own the TORREYPINES THERAPEUTICS & Design trademark, which is registered in the U.S. and in Japan, Canada, and the European Community. We also own our Tree Logo trademark, which is registered in the U.S. Additionally, we own the POSIPHEN trademark, which is registered or pending in approximately 25 countries.

To protect our trade secrets and proprietary information, we require our employees, scientific advisors, consultants and collaborators to execute confidentiality agreements when they begin to work with us. Additionally, we require our employees, scientific advisors and consultants to assign to us any inventions developed as a result of their relationship with us. While these agreements provide a certain degree of protection of our proprietary information and internally developed technologies, they do not provide protection in the event of unauthorized disclosure of such information.

Manufacturing and Supply

We currently have no manufacturing capabilities and rely, or will rely, on third parties for the preclinical or clinical supplies of each of our product candidates. We do not currently have relationships for redundant supply or a second source for any of our product candidates. However, we believe that there are alternate sources of supply that can satisfy our preclinical and clinical trial requirements without significant delay or material additional costs.

Because our product candidates are all in an early stage of development, there is no commercial process developed for the synthesis of active pharmaceutical ingredient, or API, for any of our product candidates. In addition, we have not identified final market formulations and delivery systems for any of our product candidates. We must rely upon third party vendors to achieve a final commercial process for API and we must obtain FDA approval for both the API process and the drug product. Our reliance on third party vendors may result in delays, significant and unanticipated costs, or yield lower than anticipated amounts of product.

Commercial quantities of any products we seek to develop will have to be manufactured in facilities and by processes that comply with the FDA and other regulations for current good manufacturing practices, or cGMPs. We plan to rely on third parties to manufacture commercial quantities of any products we successfully develop. We believe that there are several manufacturing sources available to us on commercially reasonable terms to meet our clinical requirements as well as any commercial production requirements.

Sales and Marketing

We currently have no marketing, sales or distribution capabilities. We may establish a small, specialty sales and marketing capability in the United States if and when we obtain regulatory approval for tezampanel for the treatment of migraine.

To market tezampanel outside of the United States, or if and when NGX426 obtains regulatory approval, or in situations or markets where a more favorable return may be realized through licensing commercial rights to a third party, we may license a portion or all of our commercial rights in a territory to a third party in exchange for one or more of the following: up-front payments, research funding, development funding, milestone payments and royalties on product sales.

Given the early stage of development, we do not have a sales and marketing plan for our xerostomia, CIAS or Alzheimer's disease product candidates. In order to participate in the commercialization of any of our products, we must develop these capabilities on our own or in collaboration with third parties. Alternatively, we may also choose to hire a third party to provide sales personnel instead of developing our own staff.

Government Regulation

FDA Requirements for New Drug Compounds

The research, testing, manufacture and marketing of pharmaceutical products are extensively regulated by numerous governmental authorities in the United States and other countries. In the United States, pharmaceutical products are subject to rigorous regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, labeling, promotion and marketing and distribution of pharmaceutical products. Failure to comply with applicable regulatory requirements may subject a company to a variety of administrative or judicial sanctions, including:

- suspension of review or refusal to approve pending applications;
- product seizures;
- recalls;
- withdrawal of product approvals;
- restrictions on, or prohibitions against, marketing its products;
- fines;
- restrictions on importation of its products;
- injunctions;
- debarment; and
- civil and criminal penalties.

The steps ordinarily required before a new pharmaceutical product may be marketed in the United States include:

preclinical laboratory tests, animal studies and formulation development according to good laboratory practices, or GLPs;

submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical, or human, testing may commence;

adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each indication for which FDA approval is sought according to good clinical practices;

submission to the FDA of a new drug application, or NDA;

satisfactory completion of an FDA Advisory Committee review, if applicable;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP; and

FDA review and approval of the NDA.

Satisfaction of FDA pre-market approval requirements typically takes several years, and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease. Government regulation may delay or prevent marketing of potential candidates for a considerable period of time and impose costly procedures upon a manufacturer's activities. Success in early stage clinical trials does not assure success in later stage clinical trials. Data obtained from clinical development is not always conclusive and may be susceptible to varying interpretations that could delay, limit or prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market.

Preclinical tests include laboratory evaluation of product chemistry and formulation, as well as toxicology studies to assess the safety of the product. The conduct of the preclinical tests and formulation of compounds for testing must comply with federal regulations and requirements. The results of preclinical testing are then submitted to the FDA as part of an IND.

An IND, which must be approved before human clinical trials may begin, will automatically become effective 30 days after the FDA receives it, unless the FDA raises concerns or questions about the IND. If the FDA has questions or concerns, they must be resolved to the satisfaction of the FDA before initial clinical testing can begin. In addition, the FDA may, at any time, impose a clinical hold on on-going clinical trials. If the FDA imposes a clinical hold, clinical trials cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA. In some instances, the IND process can result in substantial delay and additional expense.

Clinical trials involve the administration of the investigational drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated, among other things. Each protocol involving testing in the United States must be submitted to the FDA as part of the IND. In addition, an institutional review board, or IRB, at each site at which the clinical trial is conducted must approve the protocols, protocol amendments and informed consent documents for patients. All clinical trial participants must provide their informed consent in writing.

Clinical trials to support an NDA for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase I clinical trials, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess safety, including side effects associated with increasing doses, metabolism, pharmacokinetics and pharmacological actions. Phase II clinical trials usually involve trials in a limited patient population, usually several hundred people, to determine dosage tolerance and optimum dosage, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied. In certain patient populations, accelerated approval is available based on Phase II clinical trial data. A Phase IIa clinical trial is typically designed to obtain proof-of-concept data and determine if the product candidate has an effect on a limited number of patients. A clinical trial designed to generate efficacy data but that is not expected to satisfy FDA criteria for NDA approval is sometimes referred to as a Phase IIb clinical trial. If a

compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase II clinical trials, Phase III clinical trials are undertaken to further evaluate clinical safety and efficacy within an expanded patient population, usually several hundred to several thousand subjects, typically at geographically dispersed clinical trial sites. Phase I, Phase II or Phase III clinical trials of any product candidate may not be completed successfully within any specified time period, if at all.

After successful completion of the required clinical testing, generally an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of extensive preclinical studies and clinical trials and other detailed information, including, information relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA is substantial. Under federal law, the submission of NDAs are generally subject to substantial application user fees, currently exceeding $750,000, and the sponsor and/or manufacturer under an approved application are also subject to annual product and establishment user fees, currently exceeding $40,000 per product and $250,000 per establishment. Additional user fees exceeding $300,000 apply for NDA supplements containing clinical data. Fees are waived for the first pre-market application from companies with gross sales of less than $30 million. These fees are typically increased annually.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that the NDA is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under federal law, the FDA has agreed to certain performance goals in the review of most NDAs. Applications for non-priority drug products are generally reviewed within 12 months. Applications for priority drugs, such as those that address an unmet medical need, are generally reviewed within 6 months. The review process can be significantly extended by FDA requests for additional information or clarification regarding information already provided in the submission.

The FDA may also refer applications for novel drug products or drug products that 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. The FDA is not bound by the recommendation of an advisory committee. Also, before approving an NDA, the FDA will inspect the facility or the facilities at which the product is manufactured to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity.

If FDA evaluations of the NDA and the manufacturing facilities are favorable, the FDA may issue an approval letter, or, in some cases, an approvable letter followed by an approval letter. An approvable letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. If the FDA's evaluation of the NDA submission is not favorable, the FDA may refuse to approve the NDA or issue a not approvable letter. A not approvable letter outlines the deficiencies in the submission and may require additional testing or information in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. With limited exceptions, the FDA may withhold approval of an NDA regardless of prior advice it may have provided or commitments it may have made to the sponsor.

As a condition of NDA approval, the FDA may require post-approval testing and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions which can materially impact the potential market and profitability of the drug. In addition, a product approval may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

The FDA has various programs, including FastTrack designation, accelerated approval and priority review that are intended to expedite or simplify the process for reviewing certain drugs. Specifically, drug products that are intended for the treatment of serious or life-threatening conditions and demonstrate the potential to address unmet medical needs may be eligible for FastTrack designation and/or accelerated approval. Products may qualify for accelerated approval based on adequate and well-controlled Phase II clinical trial results that establish that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug product receiving FastTrack or accelerated approval perform post-marketing clinical trials. In addition, if a drug product would provide a significant improvement compared to marketed products, it may be eligible to receive priority review, which shortens the time in which the FDA acts on the sponsor's application. Even if a drug product qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or the time period for FDA review or approval will not be shortened.

After an NDA is approved, the approved drug will be subject to certain post-approval requirements, including a requirement to report adverse events and to submit annual reports. In addition, a supplemental NDA may be required for approval of changes to the originally approved indication, prescribing information, product formulation, and manufacturing and testing requirements. Following approval, drug products are required to be manufactured and tested for compliance with NDA and/or compendia specifications prior to release for commercial distributions. The manufacture and testing must be performed in approved manufacturing and testing sites that comply with cGMP requirements and are subject to FDA inspection authority.

Approved drugs must be promoted in a manner that is consistent with their terms and conditions of approval, and that is not false or misleading. In addition, the FDA requires substantiation of any claims of superiority of one product over another, generally through adequate and well-controlled head-to-head clinical trials. To the extent that market acceptance of our product candidates may depend on their superiority over existing therapies, any restriction on our ability to advertise or otherwise promote claims of superiority, or requirements to conduct additional expensive clinical trials to provide proof of such claims, could negatively affect the sales of our products and/or our expenses.

Once an NDA is approved, the product covered thereby becomes a "listed drug" which can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients, strength, dosage form, route of administration and conditions of use, and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Generally, an ANDA applicant is required only to conduct bioequivalence testing, and is not required to conduct or submit results of preclinical or clinical tests to prove the safety or efficacy of its drug product. Drugs approved in this way, commonly referred to as "generic equivalents" to the listed drug, are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, which is referred to as the Orange Book, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, indication or route of administration or combination, if one of the clinical trials conducted was essential to the approval of the application and was conducted or sponsored by the applicant. During this three year period, the FDA cannot grant effective approval of an ANDA based on that listed drug. Federal law also provides a period of exclusivity for five years following the approval of a drug containing a new chemical entity, except that an ANDA may be submitted after four years following the approval of the original product if the ANDA challenges a listed patent as invalid or not infringed.

Applicants submitting an ANDA are required to make a certification with regard to any patents listed for an innovative drug, stating that either there are no patents listed in the Orange Book for the innovative drug, any patents listed have expired, the date on which the patents will expire, or that the patents listed are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug for which the ANDA is submitted. If an ANDA applicant certifies that it believes all listed patents are invalid or not infringed, it is required to provide notice of its ANDA submission and certification to the NDA sponsor and the patent owner. If the patent owner, its representatives, or the approved application holder, who is an exclusive patent licensee, then initiates a suit for patent infringement against the ANDA sponsor within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA until either 30 months have passed or there has been a court decision holding that the patents in question are invalid or not infringed. On the other hand, if a suit for patent infringement is not initiated within the 45 days, the ANDA applicant may bring a declaratory judgment action.

If the ANDA applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA until those patents expire. The first ANDA submitting a substantially complete application certifying that all listed patents for a particular product are invalid or not infringed may qualify for a period of 180 days of exclusivity against other generics, which begins to run after a final court decision of invalidity or non-infringement or after the applicant begins marketing its product, whichever occurs first, during which time subsequently submitted ANDAs cannot be granted effective approval. If more than one applicant files a substantially complete ANDA on the same day, each such first applicant will be entitled to share the 180-day exclusivity period, but there will only be one such period, beginning on the date of the first marketing by any of the first applicants.

FDA also imposes a number of complex requirements and restrictions on entities that advertise and promote prescription drugs, which include, among others, standards for and regulations of print and in-person promotion, product sampling, direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet. The FDA has very broad enforcement authority under the Federal Food, Drug and Cosmetic Act, and failure to abide by FDA requirements can result in penalties and other enforcement actions, including the issuance of warning letters or other letters objecting to violations and directing that deviations from FDA standards be corrected, total or partial suspension of production, and state and federal civil and criminal investigations and prosecutions.

From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of drug products. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency or the courts in ways that may significantly affect our business and products candidates. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed, or what the impact of such changes, if any, may be.

Foreign Regulation of New Drug Compounds

Approval of a product by comparable regulatory authorities may be necessary in foreign countries prior to the commencement of marketing of the product in those countries, whether or not FDA approval has been obtained. In general, each country has its own procedures and requirements, many of which are time consuming, expensive, and may require additional studies prior to marketing the product. Also, the time required may differ from that required for FDA approval. Thus, there can be substantial delays in obtaining required approvals from foreign regulatory authorities after the relevant applications are filed.

In Europe, marketing authorizations may be granted at a centralized level, a decentralized level or a national level. The centralized procedure provides a single marketing authorization valid in all European Union member states, and is mandatory for the approval of most medicinal products, including certain biotechnology products. The decentralized procedure allows an applicant to seek market authorizations in several designated member states at once, and a national market authorization provides an authorization valid in only one member state. All medicinal products that are not subject to the centralized procedure and which have received at least one marketing authorization in another member state may receive additional marketing authorizations from other member states through a mutual recognition procedure.

Reimbursement and Pricing

In the United States and elsewhere, sales of pharmaceutical products depend in significant part on the availability of reimbursement to the consumer from third-party payors, such as government and private insurance plans. Third-party payors are increasingly challenging the prices charged for medical products and services. It will be time-consuming and expensive for us to go through the process of seeking reimbursement from Medicare and private payors. Our products may not be considered cost effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis.

In many foreign markets, including the countries in the European Union, pricing of pharmaceutical products is subject to governmental control. In the United States, there have been, and we expect that there will continue to be, a number of federal and state proposals to implement similar governmental pricing control. While we cannot predict whether such legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on our business, financial condition and profitability.

Hazardous Materials

Our discovery and development processes involve the controlled use of hazardous materials, chemicals and radioactive materials and the production of waste products. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous materials and waste products. We do not expect the cost of complying with these laws and regulations to be material.

Employees

As of December 31, 2007, we had 42 full-time employees, 29 of whom were engaged in research and development and 13 of whom were engaged in management, administration and finance. Of our employees, more than half hold advanced degrees. In February 2008 we reduced our workforce to 34 full-time employees, 21 of whom were engaged in research and development and 13 of whom were engaged in management, administration and finance. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Company Website

We maintain a website at *www.torreypinestherapeutics.com*. We make available free of charge on our website our periodic and current reports as soon as reasonably practicable after such reports are filed with the Securities and Exchange Commission, or SEC. Information contained on, or accessible through, our website is not part of this report or our other filings with the SEC.

We were initially incorporated in Nevada on July 29, 1997 as Axonyx Inc. In October 2006, we were reincorporated in Delaware and changed our name to TorreyPines Therapeutics, Inc. Our

principal executive offices are located at 11085 North Torrey Pines Road, Suite 300, La Jolla, CA 92037, and our telephone number is (858) 623-5665.

Item 1A. Risk Factors.

You should consider carefully the following information about the risks described below, together with the other information contained in this annual report on Form 10-K and in our other filings with the Securities and Exchange Commission, before you decide to buy or maintain an investment in our common stock. We believe the risks described below are the risks that are material to us as of the date of this annual report. If any of the following risks actually occur, our business financial condition, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of the money you paid to buy our common stock.

Risks Related to Our Business

We expect to continue to incur net operating losses for the next several years and may never achieve profitability.

We have incurred net operating losses every year since our inception. As of December 31, 2007, we had an accumulated deficit of approximately $96.4 million. Over the next several years we expect a significant increase in our operating losses as we conduct additional discovery, development, clinical testing and regulatory compliance activities. All of our revenue to date has been payments received in connection with our collaboration and licensing agreements. We cannot be certain that we will generate additional revenue through licensing activities or that we will receive any of the milestone or royalty payments associated with our current collaboration and licensing agreements. Given the risks associated with discovery, development, clinical testing, manufacturing and marketing of drug products, we may never be successful in commercializing a drug product that will enable us to be profitable. Our ability to generate significant continuing revenue depends on a number of factors, including:

successful completion of on-going and future clinical trials for our product candidates;

achievement of regulatory approval for our product candidates;

successful completion of current and future strategic collaborations; and

successful manufacturing, sales, distribution and marketing of our products.

We do not anticipate that we will generate significant continuing revenue for several years. Even if we do achieve profitability, we may not be able to sustain or increase profitability.

All of our product candidates are at an early stage of development. We cannot be certain that any of our product candidates will be successfully developed, receive regulatory approval, or be commercialized.

Our product candidates are at an early stage of development and we do not have any products that are commercially available. Our product candidates, ionotropic glutamate receptor antagonists tezampanel and NGX426 and muscarinic receptor agonist NGX267, are currently in clinical development. Our product candidate, NGX292, is in preclinical development. We will need to perform additional development work and conduct further clinical trials for all of our product candidates before we can seek the regulatory approvals necessary to begin commercial sales.

Success in preclinical testing and early clinical trials does not mean that later clinical trials will be successful. Companies frequently suffer significant setbacks in later stage clinical trials, even after earlier clinical trials have shown promising results. In future clinical trials with larger or somewhat different populations, results from early clinical trials may not be reproduced and analysis of new or

additional data may not demonstrate sufficient safety and efficacy to support regulatory approval of a product candidate.

Additionally, preclinical testing and clinical trials are expensive, can take many years, and have an uncertain outcome. Product candidates may not be successful in clinical trials for a number of reasons, including, but not limited to, the failure of a product candidate to be safe and efficacious, the results of later stage clinical trials not confirming earlier clinical results, or clinical trial results not being acceptable to the FDA or other regulatory agencies.

There is no certainty that the safety and efficacy results of our Phase IIb clinical trial for tezampanel in acute migraine announced in October 2007 are predictive of results in subsequent trials of tezampanel or are meaningful indicators of the efficacy of tezampanel. We will be required to perform additional clinical testing in order to obtain regulatory approval of tezampanel and the results of such additional clinical testing may not replicate what has been demonstrated to date regarding the safety and efficacy of tezampanel. Additionally, further testing of tezampanel may not result in data sufficient to support regulatory approval.

We do not anticipate that any of our current product candidates will be eligible to receive regulatory approval and begin commercialization for a number of years, if at all. Even if we were to ultimately receive regulatory approval for one or more of our product candidates, we may be unable to successfully commercialize them for a variety of reasons including:

- the availability of alternative treatments;
- the product not being cost effective to manufacture and sell;
- limited acceptance in the marketplace; and
- the effect of competition with other marketed products.

The success of our product candidates may also be limited by the incidence and severity of any adverse events or undesirable side effects. Additionally, any regulatory approval to market a product may be subject to the imposition by such regulatory agency of limitations on the indicated uses. These limitations may reduce the size of the market for the product. If we fail to commercialize one or more of our current product candidates, our business, results of operations, financial condition, and prospects for future growth will be materially and adversely affected.

We will need substantial additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our discovery and development programs or commercialization efforts.

We will need to raise substantial additional capital in the future and additional funding requirements will depend on, and could increase significantly as a result of, many factors, including:

- the rate of progress and cost of clinical trials;