AXONYX INC
Form 10-K
March 16, 2006

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2005

OR

o TRANSACTION 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
AXONYX INC.
500 Seventh Avenue, 10th Floor
New York, New York 10018
Telephone (212) 645-7704
I.R.S. Employer Identification Number: 86-0883978
State or Other jurisdiction of Incorporation or Organization: NEVADA
Securities registered pursuant to Section 12(g) of the Act: COMMON STOCK $0.001 PAR VALUE

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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. o

Indicate by check mark whether registrant is a large accelerated filer, an accelerated filer or a non-accelerated filer (as defined in Rule 12b-2 of the Act).
Large accelerated filer o Accelerated filer x Non-accelerated filer o

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

The aggregate market value of the Common Stock held by non-affiliates as of June 30, 2005 (calculated using the closing price on that date on NASDAQ of $1.33 per share) was approximately $67,840,000.

The number of shares of Common Stock, par value $0.001, of the Registrant outstanding as of March 15, 2006, was 53,680,721 shares.

DOCUMENTS INCORPORATED BY REFERENCE: NONE

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This Form 10-K contains forward-looking statements, as defined in the Private Securities Litigation Reform Act of 1995 that are based on current expectations, estimates and projections. Statements that are not historical facts, including statements about our beliefs and expectations, are forward-looking statements. These statements involve potential risks and uncertainties; therefore, actual results may differ materially. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date on which they were made. We do not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

The statements represent our judgment to date, and are subject to risks and uncertainties that could affect the Company, including those risks and uncertainties described in the documents Axonyx files from time to time with the SEC. Specifically, with respect to our drug candidates Phenserine, Posiphen and Bisnorcymserine, Axonyx cannot assure that: any preclinical studies or clinical trials, whether ongoing or conducted in the future, will prove successful, and if successful, that the results can be replicated; safety and efficacy profiles of any of its drug candidates will be established, or if established, will remain the same, be better or worse in future clinical trials, if any; pre-clinical results related to cognition and the regulation of beta-APP will be substantiated by ongoing or future clinical trials, if any, or that any of its drug candidates will be able to improve the signs or symptoms of their respective clinical indication or slow the progression of Alzheimer s disease; any of its drug candidates will support an NDA filing, will be approved by the FDA or its equivalent, or if approved, will prove competitive in the market; or that Axonyx will have or obtain the necessary financing to support its drug development programs. Axonyx cannot assure that it will be successful with regard to identifying a (sub-)licensing partner for any of its compounds, or that any that such partner will successfully develop or commercialize any of such compounds. Axonyx undertakes no obligation to publicly release the result of any revisions to such forward-looking statements that may be made to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events.

We do not undertake to discuss matters relating to our ongoing clinical trials or our regulatory strategies beyond those which have already been made public or discussed herein.

PART I

Item 1. Business

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A. Recent Events

Advances and milestones with our drug development programs

We currently have three compounds in development for Alzheimer s disease (AD): Phenserine, a potential symptomatic and disease progression treatment for mild to moderate AD; Posiphen , a potential disease progression treatment for AD; and Bisnorcymserine (BNC), a potential symptomatic treatment for severe AD. See Item 1, Section B, Axonyx Business Strategy and Drug Development Programs.

In February 2005, we announced the top line outcome of our first Phase III clinical trial with Phenserine in 375 patients exhibiting mild to moderate AD. The trial showed that although there were encouraging trends with both Phenserine 10mg and 15mg twice daily, overall these did not result in a statistically significant improvement over placebo for the protocol s primary endpoints following 26 weeks of treatment. The trial did not reveal any adverse events, safety or tolerability concerns. At that time we halted additional patient recruitment for the second and third Phase III clinical trials in order to evaluate the planned Phenserine clinical program following recommendations from the Company s Scientific Advisory Board and Safety Steering Committee.

In July 2005, we conducted a second interim statistical analysis of 59 patients from a then ongoing Phase IIb double-blind placebo-controlled clinical trial (AX-CL-06a). This trial was designed to evaluate the effects of Phenserine tartrate treatment for 6 months on plasma and cerebrospinal fluid (CSF) levels of beta-amyloid (Aβ 1- 42) and other biomarkers in mild to moderate AD patients. While this second interim analysis appeared to again confirm that Phenserine could have a beneficial effect on the levels of beta-amyloid, definitive conclusions could not be drawn due to the variability of the data.

In August 2005, the U.S. Food and Drug Administration (FDA) approved our Investigational New Drug (IND) application, submitted in June 2005, allowing Phase I clinical testing of Posiphen . The first Phase I clinical study primarily evaluated the safety of single ascending doses of Posiphen in healthy volunteers.

In September 2005, we announced top line results of an analysis of the two curtailed Phase III clinical trials (AX-CL-09/010) with Phenserine. Results following 12 weeks of treatment, as measured by the AD Assessment Scale, cognitive subscale (ADAScog) and Clinical Interview Based Impression of Change with caregiver input (CIBIC+), did not demonstrate a statistically significant benefit of Phenserine treatment over placebo. Patient recruitment for these studies had previously been halted and the planned 26-week treatment period shortened based on previously released results of a 375-patient trial (AX-CL-06) [see above] which had showed no statistically significant differences between Phenserine and placebo. There were no safety or tolerability concerns associated with Phenserine treatment.

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In November 2005, we announced the results of an additional analysis of a subgroup of 188 patients from the two curtailed Phase III clinical trials (AX-CL-09/010) with Phenserine. The subgroup of patients, who received Phenserine 15mg twice daily, demonstrated a statistically significant benefit over placebo as measured by ADAS-cog, when treated for more than 12 weeks. Additionally, this subgroup showed a positive trend towards improvement in CIBIC+ test, which approached statistical significance. There were no unexpected safety or tolerability concerns associated with Phenserine treatment. This analysis was undertaken in addition to the previously announced results of the primary pre-defined statistical analysis.

In January 2006, we announced that we had granted to Daewoong Pharmaceutical Company Ltd. (Daewoong) an exclusive license for the use of Phenserine in the South Korean market. Under the terms of the agreement Daewoong, at its own cost, undertakes to pursue the product development and regulatory work necessary for a New Drug Application (NDA) (or its equivalent) in South Korea with respect to Phenserine for the treatment of AD. The financial terms of the deal include royalty payments to us based on sales of Phenserine by Daewoong in the South Korean market.

In January 2006, we announced the completion of a single ascending dose Phase I trial with Posiphen , in clinical development for the treatment of AD progression. This double-blind, placebo controlled study of Posiphen in healthy men and women sought to establish well tolerated doses. Posiphen appears to be well tolerated at single doses up to and including 80mg. Blood levels of Posiphen associated with this study were higher than those associated with beneficial effects on beta-amyloid metabolism in animal models. The build-up of beta-amyloid (Aβ) is generally believed to be causative of the dementia of AD. No serious adverse events were reported at any dose level.

We announced in January of 2006 that three presentations of data on our drug development candidate, Phenserine, and one presentation of data on our drug development candidate, Posiphen , will be made at the 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy in Geneva, Switzerland, being held April 19-22, 2006.

In February 2006, we reported a statistically significant reduction in the plasma levels of beta-amyloid 1- 42 (AB-42) in healthy subjects treated with Phenserine for 35 days, in a previously conducted Phase I study.

Recent Board and Management Changes

In March of 2005 we announced that Marvin S. Hausman, MD had stepped down as Chief Executive Officer and that Gosse B. Bruinsma MD has been unanimously appointed by the Board of Directors to this position. Dr. Hausman continued to serve as Chairman of the Board. Dr. Bruinsma joined Axonyx in 2000 as President of Axonyx Europe BV based in the Netherlands. In April 2001 Dr. Bruinsma was promoted to Chief Operating Officer and in September 2003 he became our President.

In May 2005, we appointed Steven B. Ratoff to the Board of Directors. Mr. Ratoff replaced Michael A. Griffith, who resigned from the Board on April 29, 2005 in order to fully pursue a new business venture he is leading.

In June 2005, we announced that Marvin S. Hausman, MD, would step down as Chairman on September 14, 2005 but would remain a director of our board. The board of directors unanimously elected Steven B. Ratoff as non-executive Chairman to succeed Dr. Hausman.

In June 2005, we appointed Paul Feuerman as our General Counsel. Mr. Feuerman is a founding member of PharmAdvisors LLC, a consulting firm serving pharmaceutical and biopharmaceutical companies. Formerly, he was Executive Vice President and General Counsel of Schein Pharmaceutical Inc., a New York Stock Exchange listed specialty pharma/generics company.

Other Recent Events

In May of 2005, we approved the adoption of a shareholder rights plan. The shareholder rights plan was designed to ensure that shareholders realize fair value and equal treatment in the event of an attempted takeover of

the Corporation and to protect the Corporation and its shareholders against coersive takeover tactics. The plan was not adopted as a result of any existing or proposed potential takeover threat.

In December 2005 we received notice from The NASDAQ Stock Market, Inc. that the minimum bid price of the Company s common stock had fallen below $1.00 for 30 consecutive business days and that we were therefore not in compliance with NASDAQ Marketplace Rule 4310(c)(4). On March 8, 2006 we received a letter from NASDAQ that we had regained compliance with the $1.00 per share minimum bid price requirement for continued listing on the NASDAQ Capital Market.

B. Axonyx Business Strategy and Drug Development Programs

We are a biopharmaceutical company, specializing in central nervous system (CNS) neurodegenerative diseases, engaged in the business of acquiring patent rights to clinical stage compounds, compounds with strong proof of concept data and compounds ready for proof of concept validation with convincing scientific rationale, or potentially another company with similar rights. We further develop and add value to these compounds and then seek to out-license or partner them when we believe it business prudent. We have acquired patent rights to three main classes of therapeutic compounds designed for the treatment of AD, Mild Cognitive Impairment, and related diseases. We have acquired patent rights to a class of potential therapeutic compounds designed for the treatment of prion related diseases, which are degenerative diseases of the brain that are thought to be caused by an infectious form of a protein called a prion. Prions, unlike viruses, bacteria and fungi, have no DNA and consist only of protein. Such diseases include Creutzfeldt Jakob Disease, new variant in humans, Bovine Spongiform Encephalopathy (BSE or Mad Cow Disease) in cows, and Scrapies disease in sheep. We have licensed these patent rights from New York University. We also have co-ownership rights to patent applications regarding the therapeutic compound named Posiphen designed for the treatment of AD progression and Bisnorcymserine (BNC) in development for the treatment of severe AD.

Our mission is to be a leading biopharmaceutical company that develops products and technologies to treat central nervous system disorders. Our initial business strategy has been focused primarily on three compounds in development for AD. These are:

Phenserine A symptomatic and disease progression treatment of mild to moderate AD

Posiphen A disease progression treatment for AD

Bisnorcymserine (BNC) A symptomatic treatment of severe AD

Our current business strategy includes identifying and seeking to in-license potential compounds or partner with companies to expand our product development portfolio.

Phenserine is an inhibitor of acetylcholinesterase for the potential treatment of mild to moderate AD. Acetylcholinesterase is an enzyme active in the nerve synapse that degrades the neurotransmitter acetylcholine in the brain and other tissues of the body. Acetylcholinesterase inhibitors are drugs designed to selectively inhibit acetylcholinesterase. Acetylcholine is a chemical substance that sends signals between nerve cells, called neurotransmission, and is therefore called a neurotransmitter. Neurotransmitters are secreted by neurons, or nerve cells, into the space between neurons called the synapse. Acetylcholine is a primary neurotransmitter in the brain, and is associated with memory and cognition. Inhibition of its breakdown in AD patients has been shown to improve memory and cognition.

Posiphen is a compound that appears to decrease the formation of the beta amyloid precursor protein (beta-APP) and amyloid with potential applications in the treatment of AD progression. Posiphen is the positive isomer of Phenserine. As such, it appears to affect the messenger RNA of beta-APP as well as inhibit beta secretase whereby levels of neurotoxic beta amyloid, in preclinical animal models, are reduced.

Bisnorcymserine is a butyrylcholinesterase inhibitor. Butyrylcholinesterase is found in high concentration in the plaques taken from individuals who have died from AD. Butyrylcholinesterase is an enzyme that is normally found widely in the body and butyrylcholine appears to play a relatively increasingly important role in advancing AD. Inhibition of the enzyme may prove valuable in the treatment of severe AD.

The Phenserine Development Program

Our most advanced compound, Phenserine, selectively inhibits acetylcholinesterase, the enzyme primarily responsible for degrading acetylcholine at the synaptic gap between neurons, thus increasing the availability of this neurotransmitter. Phenserine has been shown to be a potent and selective inhibitor of this enzyme in the rat brain and increases memory and learning over a wide therapeutic dosage range in aged rats without causing toxic side effects. The compound readily enters the brain, has minimal activity in other organs outside the brain, and has a long duration of action. In pre-clinical studies, Phenserine was shown to have a brain to blood ratio of 10:1. Increasing the concentration of the active drug agent in the brain versus the rest of the body potentially maximizes the effects of the drug while potentially reducing peripherally mediated side effects.

Phenserine also has been shown to have the ability to inhibit the formation of the beta-amyloid precursor protein (beta-APP), a large protein that is the source of the neurotoxic peptide, beta amyloid. By inhibiting the formation of beta-APP, Phenserine can decrease the presence of the soluble beta amyloid protein that is potentially deposited in the brain as amyloid plaques, apparently causing eventual neuronal cell death. These studies were conducted at laboratories at the National Institute of Aging (NIA) in human neuroblastoma cell cultures and *in vivo* in rodents. Studies in human neuroblastoma cell lines showed that the compound reduces the formation of beta-amyloid peptide. Neuroblastoma cell cultures are a type of cell derived from the human brain that can be grown in containers in the lab (*in vitro*) where they are able to reproduce and carry out many activities as if they were residing in the brain, including the synthesis and secretion of proteins such as the beta-amyloid protein which, in the human brain, can form plaques. A neuroblastoma cell culture is used to study brain cell function in a simple *in vitro* system, which allows testing of the ability of drugs to prevent the formation of the beta-amyloid precursor protein and secretion of beta amyloid. Additional animal studies using the transgenic mouse have confirmed these findings. The transgenic mouse is a bio-engineered animal that mimics hallmark pathologic changes that occur in the human AD brain. These results suggest that Phenserine may have the ability to slow the progression of AD in addition to providing symptomatic relief for the cognitive changes.

In December 1999, we initiated Phase I human clinical trials for Phenserine utilizing healthy elderly patients at a U.S. research center. These Phase I safety and tolerance trials involving both single and multiple ascending doses were successfully completed in September 2000.

In October 2001, we completed a Phase II proof-of-concept double-blind placebo-controlled clinical trial with Phenserine in AD patients. This Phase II proof-of-concept trial was designed to determine the drug s safety and possibly a trend toward efficacy in patients exhibiting mild to moderate AD. The trial included 72 patients, with 48 patients receiving two daily doses of Phenserine 10mg and 24 patients received a placebo. The safety results from the trial substantiated Phase I results indicating that the drug is safe and well tolerated. Although the trial was not of the duration necessary and did not include the number of patients required to detect statistically significant clinical improvement in efficacy, nevertheless certain memory tests showed statistically significant results while other tests showed a trend towards statistical significance.

To date, we have conducted the following Phase III clinical trials with Phenserine: AX-CL-06/06e, AX-CL-09, AX-CL-010, as well as a Phase IIb trial, AX-CL-06a.

Protocol AX-CL-06 was a double-blind, placebo controlled trial initiated in June 2003 comparing the efficacy and tolerability of Phenserine 10mg or 15mg twice daily doses with twice daily placebo in patients who met the diagnostic criteria for probable mild to moderate AD. Two different regimens, 10mg twice daily and 15mg twice daily, were compared with placebo in this trial. The randomization was 1:2:2 for placebo: 10mg twice daily: 15mg twice daily. Patients randomized to active treatment were started on a 5mg twice daily regimen for the first month of treatment. This was increased to 10mg twice daily for the second month of treatment. The dose was increased to 15mg twice daily during the third month for patients randomized to the highest dose regimen. Once a patient reached his or her target dose, it was maintained for a total treatment duration of 26 weeks. Patients who could not tolerate their target dose were discontinued. Discontinued patients were not replaced. A total of 384 patients were enrolled in the study. Of these, 377 received treatment. The remaining 7 never received drug treatment so they were excluded from the data analyses.

The primary efficacy variables were the ADAS-Cog and CIBIC+. The Phenserine groups showed consistently greater improvement in ADAS-Cog and CIBIC+ scores than the placebo group although the differences did not achieve statistical significance.

Protocol AX-CL-06a was a double-blind placebo controlled study of the effect of Phenserine 10- or 15mg twice daily on cerebrospinal and plasma amyloid peptides from baseline and, at 26 weeks, initiated in June 2003. Although both doses of Phenserine tended to lower beta amyloid peptides more than placebo, none of the differences achieved statistical significance.

Protocol AX-CL-06e was an open-label extension to studies AX-CL-06 and AX-CL-06a that allowed all patients who had successfully completed either trial to continue on Phenserine 15mg twice daily dose for up to an additional six months. This extension was to gather additional safety data on Phenserine treatment.

Protocol AX-Cl-09/010, initiated in the second half of 2004, was originally initiated as two identical 26-week placebo controlled trials of 450 AD patients each. During the implementation of the studies, results of Protocol AX-CL-06 became available. The results of this earlier study showed a numerical benefit of Phenserine treatment relative to placebo but failed to achieve statistical significance. Based on these results, enrollment in the two ongoing studies was halted at 255 patients in total, and the primary endpoint analysis was shortened to 12 weeks. Because the individual curtailed studies were underpowered, their data were combined and analyzed as a single trial. This was a randomized, multinational, multicenter placebo-controlled parallel-group study. Because the study was curtailed, many patients did not reach the originally scheduled 26-week end of treatment. However, all patients were allowed to complete at least 12 weeks of therapy. Patients were screened within 21 days of entry and randomly assigned to receive 10 or 15 mg of Phenserine twice daily or placebo. A titration schedule was used so that patients randomized to active treatment received 5mg twice daily for the first 4 weeks of the study followed by 10mg twice daily for 4 weeks. Patients randomized to 15mg twice daily received this dose starting in the ninth week. Treatment at the assigned doses was continued for up to 26 weeks. At the 12-week visit, patients randomized to 10mg twice daily had received this dose for approximately 8 weeks. Patients randomized to receive 15mg twice daily had received this dose for approximately 4 weeks.

Although the study did not achieve statistical significance in its primary endpoints, a subgroup of patients, who received Phenserine 15mg twice daily, demonstrated a statistically significant benefit over placebo as measured by the Alzheimer s Disease Assessment Scale-cognitive subscale (ADAS-cog), when treated for more than 12 weeks. Additionally, this subgroup showed a positive trend towards improvement in the Clinical Interview Based Impression of Change (CIBIC+) test, which approached statistical significance. There were no unexpected safety or tolerability concerns associated with Phenserine treatment.

We have comprehensive data sets on Phenserine having completed extensive manufacturing scale-up, preclinical studies and taken the drug into three Phase III clinical trials for mild to moderate AD. The remaining work to be done prior to an NDA submission for Phenserine is the completion of two pivotal Phase III trials. The Company has determined that it will not commit further resources to these Phase III trials, and is seeking to identify strategic partners that are able and willing to commit the necessary financial resources to Phenserine s further development and marketing approval.

In January 2006, we announced that we had granted to Daewoong Pharmaceutical Company Ltd. (Daewoong) an exclusive license for the use of Phenserine in the South Korean market. Under the terms of the agreement Daewoong, at its own costs, undertakes to pursue the product development and regulatory work necessary for a New Drug Application (NDA) (or its equivalent) in South Korea with respect to Phenserine for the treatment of AD. The financial terms of the deal include royalty payments to us based on sales of Phenserine by Daewoong in the South Korean market.

The Posiphen Development Program

Posiphen is the positive isomer of Phenserine. It appears to decrease the formation of beta-amyloid with potential application in the treatment of AD progression. Posiphen s mechanism of action is potentially through RNA translational inhibition as well as beta secretase inhibition. Posiphen has been shown to lower beta amyloid precursor protein (beta-APP) and beta-amyloid levels in pre-clinical studies. The primary mechanism of action

results in a dose dependent reduction of beta-amyloid, which may result in slowing AD progression. The initial pre-clinical side effect rates potentially allow for higher clinical doses. On August 1, 2005 we announced that the US Food and Drug Administration (FDA) approved our investigational new drug (IND) application allowing Phase I clinical testing of Posiphen . The first Phase I single ascending dose clinical study commenced in August 2005 and evaluated the safety of Posiphen in healthy volunteers.

In January 2006, we completed a single ascending dose Phase I trial with Posiphen . This double-blind, placebo controlled study of Posiphen in healthy men and women sought to establish well tolerated doses. Posiphen appears to be well tolerated at single doses up to and including 80mg. Blood levels of Posiphen associated with this study were higher than those associated with beneficial effects on beta-amyloid metabolism in animal models. The build-up of beta-amyloid (Aβ) is generally believed to be causative of the dementia of AD. No serious adverse events were reported at any dose level. We anticipate initiating a Phase I multiple ascending dose study in the first quarter of 2006.

The Bisnorcymserine Development Program

Our butyrylcholinesterase inhibitor compounds are designed to selectively inhibit butyrylcholinesterase, an enzyme similar to acetylcholinesterase. Normally these two enzymes coexist throughout the body, with acetylcholinesterase predominating in degrading acetylcholine. In the brain of AD patients, as acetylcholinesterase levels gradually fall, there appears to be a concomitant increase in butyrylcholinesterase levels in specific nerve pathways within the cortex and the hippocampus, areas associated with AD. Like acetycholinesterase, butyrylcholinesterase degrades acetylcholine at the synaptic gap between neurons, decreasing the availability of this key neurotransmitter. This enzyme was identified as a target for inhibition in AD as it also terminates the action of the neurotransmitter acetylcholine in specific nerve pathways in regions of the brain associated with AD and is found in high concentration in amyloid plaques in the brains of AD patients. Our butyrylcholinesterase inhibitor compounds act to counter butyrylcholinesterase, thus enhancing the availability of acetylcholine, potentially improving memory and cognition. Inhibition of butyrylcholinesterase may also reduce any increased toxicity of beta-amyloid caused by the presence of butyrylcholinesterase in amyloid plaques.

Several butyrylcholinesterase inhibitor drug candidates, including Bisnorcymserine, have been studied extensively in pre-clinical studies and have been found to have many of the characteristics desirable for use in AD. Like Phenserine, these compounds have a dual mechanism of action in that, in addition to inhibiting the butyrylcholinesterase enzyme, they also inhibit the formation of beta-APP in cell culture, and in rats. These pre-clinical findings indicate that these butyrylcholinesterase inhibitor compounds may have an important role in preventing the formation of amyloid plaques in AD, in addition to its inhibition of butyrylcholinesterase. The compounds readily enter the brain, they have a long duration of action and are highly active in improving memory and learning in the aged rat. Currently it appears that Bisnorcymserine has several advantages over the other compounds in pre-clinical results. Bisnorcymserine appears to be the most potent butyrylcholinesterase inhibitor in our patent portfolio. It has a 100-fold selectivity over acetylcholinesterase. Behavioral work shows it to improve memory in rodent models, and it reduces beta-APP in tissue cultures. Bisnorcymserine has three potential uses: (1) as an inhibitor of butyrylcholinesterase, (2) as an inhibitor of the production of beta-APP, thus inhibiting the formation of amyloid plaques, and (3) as an early diagnostic marker.

Bisnorcymserine (BNC) is a highly selective butyrylcholinesterase inhibitor. Butyrylcholinesterase is found in high concentration in the plaques taken from individuals who have died from AD. Butyrylcholinesterase appears to have an increasing role with advancing AD and its primary mechanism of action results in a dose dependent reduction of acetylcholine. The initial pre-clinical side effect rate potentially allows higher clinical doses. A secondary mechanism of action is associated with dose dependent reductions of beta APP and amyloid beta. BNC, the lead compound from our butyrylcholinesterase family, is currently in full pre-IND development and we plan an IND submission in second quarter 2006 followed by the potential to initiate Phase I clinical trials thereafter. A recently published article in the Proceedings of the National Academy of Science describes the underlying mechanism, in vitro and cognition results in animal models.

Other Acetylcholinesterase Inhibitors

We have assessed certain properties of our other inhibitors of acetylcholinesterase such as Tolserine, which may ultimately prove to have certain additional advantages for use in AD, and Thiatolserine, a compound that

has characteristics that may be suitable for development as a transdermal agent, one that is absorbed through a patch placed on the skin.

Other Compounds in the Axonyx Drug Portfolio

There are other potential pharmaceutical compounds that we have patents rights to that may be further developed in the future, given sufficient financial resources.

Other Pertinent Information

In December 2000, we incorporated Axonyx Europe BV, a wholly owned subsidiary, in the Netherlands. Gosse Bruinsma, M.D., currently the President and Chief Executive Officer of Axonyx Inc., is also the President of Axonyx Europe BV. To date the majority of our clinical development activities and a significant amount of our pre-clinical development activities have been carried out in Europe. The Axonyx Europe BV office manages, directs, and controls these activities. Axonyx Europe BV explores and pursues in-licensing and out-licensing opportunities for our licensed technologies and facilitates communication with our European shareholders.

We have incurred negative cash flows from operations since our inception in 1997. Our net losses for the three fiscal years ended 2003, 2004 and 2005 were $8,106,000, $28,780,000 and $28,614,000, respectively.

Axonyx Inc. was incorporated in Nevada on July 29, 1997. Our principal executive offices are located at 500 Seventh Avenue, 10th Floor, New York, New York 10018, and our telephone number is (212) 645-7704.

C. Alzheimer s Disease Overview

Axonyx Drug Development Programs

We are currently focusing on the development for Posiphen , a potential disease progression treatment for AD; and Bisnorcymserine (BNC), a potential symptomatic treatment for severe AD. We are seeking a licensing partner for our lead acetylcholinesterase inhibitor, Phenserine. See Item 1, Section B Axonyx Business Strategy and Drug Development Programs. In addition, we are sponsoring basic research at the medical University of South Carolina and the University of Indiana in the area of amyloid production and metabolism.

General

AD is a degenerative brain disease that, with individual variations, advances from memory lapses to confusion, personality and behavior changes, communication problems and impaired judgment. Over time, AD patients become increasingly unable to care for themselves, and the disease eventually leads to death. It is estimated that more than 4 million Americans and 12 million people worldwide suffer from AD. Risk factors for the disease include age and family history. According to the Alzheimer s Association, the disease affects one in 10 persons over 65 and half of those over 85 years old are affected by the disease.

While scientists are not completely certain of the specific causes of Alzheimer s, scientific discoveries have identified important hallmarks of the disease. Two schools of thought in the scientific community have been historically divided between those that believe that the neurofibrillary tangles composed of tau protein within the nerve cells are responsible for the disease and those that believe that neurotoxic beta amyloid and the senile plaques composed of beta-amyloid protein are the cause. Both neurofibrillary tangles within brain nerve cells and extracellular senile amyloid plaques in the cholinergic nerve pathways of the brain have been linked to the death of nerve cells in AD patients. Recent research indicates that a disruption or an abnormality in beta-amyloid metabolism and the formation of amyloid plaques are most likely to be the primary causes of AD.

According to the most widely accepted theory concerning the cause of AD, there are two important events leading to the formation of beta-amyloid plaques. The first event involves the abnormal processing of the beta-amyloid precursor protein (beta-APP). In AD, beta-APP is sequentially cleaved into pieces by two enzymes, creating protein fragments, one of which is the beta-amyloid peptide. The second key event is the conversion of beta-amyloid into insoluble beta-sheets that aggregate to form insoluble fibrous masses (fibrils). These fibrils are deposited as part of the neurotoxic amyloid plaques that appear to cause the death of neurons in the brain. The beta-amyloid protein is a protein normally found in the brain and appears to be over-produced in AD and is considered the toxic agent responsible for neuronal cell death. There are a number of strategies for preventing the formation of

these amyloid plaques: (1) preventing the formation of beta-amyloid through the inhibition of the processing of its parent molecule, beta APP, (2) inhibiting the enzymes that cleave the beta-APP, (3) removing beta-amyloid from the brain or preventing its aggregation into plaques, and (4) the disassembly of the existing amyloid plaques.

AD is characterized by increasing cognitive impairment and progressive loss of memory. These impairments are caused, over time, by a loss of neurons of the cholinergic system of the brain and a loss of cortically-projecting neurons that connect the mid-brain with the cortical areas in the forebrain, particularly affecting brain areas associated with memory and learning. The cholinergic system is also called the parasympathetic nervous system; it is involved in nerve transmission related to memory and cognition, as well as the involuntary functioning of major organs such as the heart, lungs and gastrointestinal system. Cortically-projecting neurons are the nerve cells that connect the mid-brain to the cortical areas in the front part of the brain where nerve cells involved in memory and cognition are concentrated. In AD, the loss of these connecting nerve cells results in a reduction in the amount of the neurotransmitter acetylcholine, and the loss of mental capacity or cognition. Under normal healthy conditions, the neurotransmitter acetylcholine is produced by cholinergic neurons and released to carry messages to other cells, then broken down for reuse. The production and transmission of signals across neurons by acetylcholine is responsible, at least in part, for our memory, learning and cognitive functions. Having caused a signal to be passed from one neuron to the next, acetylcholine is subsequently broken down by an enzyme called acetylcholinesterase. In AD, the loss of these cholinergic neurons results in the decreased synthesis and availability of acetylcholine. By inhibiting acetylcholinesterase, the amount of available acetylcholine to carry messages between surviving neurons is increased, leading to improvements in memory and cognition.

Recent research suggests that for specific nerve pathways within the brain of AD patients the presence of the enzyme butyrylcholinesterase increases relative to acetylcholinesterase. Normally these two enzymes coexist throughout the body, with acetylcholinesterase predominating in degrading acetylcholine. Butyrylcholinesterase is additionally found in many other body tissues and functions to degrade a number of drugs such as codeine. In the brain of AD patients, as acetylcholinesterase levels gradually fall there is a parallel increase in butyrylcholinesterase levels in specific nerve pathways within the cortex and the hippocampus, areas associated with AD. Like acetylcholinesterase, butyrylcholinesterase degrades acetylcholine at the synaptic gap between neurons, decreasing the availability of this key neurotransmitter. Research in cell culture studies indicates that the increase in butyrylcholinesterase activity amplifies the toxicity of beta amyloid. This enzyme was identified as a target for inhibition in AD as it also terminates the action of the neurotransmitter acetylcholine in specific nerve pathways in regions of the brain associated with AD and is found in high concentration in amyloid plaques in the brains of AD patients.

In addition to inhibiting key enzymes associated with the neural transmission of acetylcholine in pre-clinical studies conducted by the National Institutes of Aging (NIA) and other independent laboratories, the acetylcholinesterase inhibitor Phenserine, Posiphen and our butyrylcholinesterase inhibitors appear to have the ability to inhibit the formation of beta-APP and to reduce levels of the beta-amyloid peptide, the primary component of amyloid plaques.

The treatment of people with AD is a multi billion-dollar industry in the United States alone and constitutes an extremely large and continually expanding potential market with an unmet therapeutic need. Currently there are four drugs that have been approved in the United States that provide symptomatic relief for one aspect of AD, inhibition of acetylcholinesterase: Cognex® (developed by Warner Lambert), Aricept® (Pfizer and Eisai), Exelon® (Novartis) and Reminyl® (Johnson & Johnson). One of the our compounds, Phenserine, is also an acetylcholinesterase inhibitor. Unlike the other marketed compounds Phenserine has demonstrated, in pre-clinical testing utilizing transgenic mice, the ability to inhibit the formation of beta-APP and to reduce levels of the beta-amyloid peptide, the primary component of amyloid plaques. Our butyrylcholinesterase inhibitor drug candidates attack the disease in other potentially effective ways, representing a potentially new platform technology for the treatment of AD.

Given the complexity of the disease, and uncertainty concerning the specific mechanisms causing AD, it appears likely that a multi-drug approach to treating the disease will be utilized in the future. We believe that safe and effective drugs could potentially be prescribed in order to attack the disease through a number of different mechanisms of action.

D. Out-Licensed Technology

Under a License Agreement with Applied Research Systems ARS Holding N.V. (ARS), a wholly owned subsidiary of Serono International, S.A. (Serono) effective September 15, 2000, we granted to ARS a sublicense of our patent rights and know-how regarding the development and marketing of the Amyloid Inhibitory Peptide (AIPs) and the Prion Inhibitory Peptide (PIPs) technology which had been licensed to us under a Research and License Agreement with New York University. See Item 1, Section G Business, Strategic Alliances. We are negotiating a re-acquisition of those rights from ARS and an option to license, on a non-exclusive basis, certain Serono patents, technology and know-how related to AIPs and PIPs. If we exercise this option and acquire the license, we would be obligated to pay to Serono an upfront payment and under certain circumstances additional milestone payments and royalties would be due.

In January 2006, we announced that we had granted to Daewoong Pharmaceutical Company Ltd. (Daewoong) an exclusive license for the use of Phenserine in the South Korean market. Under the terms of the agreement Daewoong, at its own cost, undertakes to pursue the product development and regulatory work necessary for a New Drug Application (NDA) (or its equivalent) in South Korea with respect to Phenserine for the treatment of AD. The financial terms of the deal include royalty payments to us based on sales of Phenserine by Daewoong in the South Korean market.

E. Competition

We compete with many large and small pharmaceutical companies that are developing and/or marketing drug compounds similar to those being developed by us, especially in the area of acetylcholinesterase inhibitors and the amyloid cascade. Many large pharmaceutical companies and smaller biotechnology companies have well funded research departments concentrating on therapeutic approaches to AD. We expect substantial competition from these companies as they develop different and/or novel approaches to the treatment of AD. Some of these approaches may directly compete with the compounds that we are currently or are considering developing.

In the intense competitive environment that is the pharmaceutical industry, those companies that complete clinical trials, obtain regulatory approval and commercialize their drug products first will enjoy competitive advantages. We believe that the compounds covered by our patent rights have characteristics that may enable them, if fully developed, to have a market impact.

A number of major pharmaceutical companies have programs to develop drugs for the treatment of AD. Like Phenserine, many of these drugs are acetylcholinesterase inhibitors. Warner-Lambert (Cognex®), Eisai/Pfizer (Aricept®), Novartis (Exelon®) and, most recently, Johnson & Johnson (Reminyl®), have marketed compounds of this type in the United States. Cognex® was effectively removed from the market in 1998 due to severe side effects and Aricept (donepezil) currently dominates the market with approximately $1 billion in U.S. sales in 2003. Several other pharmaceutical companies have acetylcholinesterase inhibitors in human clinical trials. In addition, Forest Laboratories Namenda™ (memantine HCl) was recently approved in the USA for the treatment of moderate to severe AD as monotherapy or in combination with donepezil, a commonly prescribed acetylcholinesterase inhibitor. Memantine has a different mechanism of action that is focused on the glutamate pathway and can potentially also be prescribed together with Phenserine and our other drug candidates in development.

Several biotechnology companies have drugs in clinical trials that are based on a beta-amyloid approach to the treatment of AD. In addition, other small biotechnology companies appear to be pursuing studies on the amyloid inhibitory peptide approach similar in scope and direction as that we had sub-licensed to Serono. Another company is developing ways to inhibit plaque deposition by interfering with the transporter molecules that carry beta-amyloid from the cell membrane, where it is produced from APP, to the cell exterior where the amyloid plaques are formed. Several pharmaceutical companies are working on compounds designed to block the secretase enzymes involved in beta-APP processing. Elan Pharmaceuticals, the California based subsidiary of the Elan Corporation of Dublin, Ireland, continues research and development work on a vaccine designed to cause the immune system to mount antibodies against the amyloid proteins that make up amyloid plaques. This work is in conjunction with Wyeth. This vaccine showed efficacy in genetically altered mice but Phase II human clinical trials were suspended by Elan due to the incidence of side effects in some patients.

In the area of butyrylcholinesterase inhibition, Novartis drug Exelon® is a dual inhibitor of both acetylcholinesterase and butyrylcholinesterase.

Many other pharmaceutical companies are developing pharmaceutical compounds for the treatment of AD or other memory or cognition impairments based on other therapeutic approaches to the disease. These drugs could become competitors for, or have additive, synergistic clinical effects with one or more of our AD targeted drug candidates. Examples of those competitive approaches include pharmaceutical compounds designed to stimulate glutamate receptors involved in memory and learning, target nicotinic and muscarinic receptors to increase the release of certain neurotransmitters, activate nerve regeneration, magnify the signals reaching aging neurons from other brain cells, and to modulate GABA (a neurotransmitter) receptors.

In the field of prions, and prion-related diseases, one company, Prionics, A.G., of Zurich, Switzerland, has a diagnostic test for animal use that is approved in Europe. Prionics is also researching the treatment of nvCJD in humans. Two other companies have veterinary diagnostic tests for Bovine Spongiform Encephalopathy (BSE) approved in the European Union and two additional companies are developing such diagnostic tests.

F. Government Regulation

Regulation by governmental authorities in the United States and foreign countries is an important factor in the development, manufacture and marketing of our proposed products. It is expected that all of our products will require regulatory approval by governmental agencies prior to their commercialization. Human therapeutic products are subject to rigorous pre-clinical and clinical testing and other approval procedures by the Food and Drug Administration (FDA) and similar regulatory agencies in foreign countries.

Pre-clinical testing is conducted on animals in the laboratory to evaluate the potential efficacy and the safety of a potential pharmaceutical product. The results of these studies are submitted to the FDA as a part of an Investigational New Drug (IND) application, which must be approved before clinical testing in humans can begin in the USA. Typically, the clinical evaluation process involves three phases. In Phase I, clinical trials are conducted with a small number of healthy human subjects to determine the early safety profile, the pattern of drug distribution and metabolism. In Phase II, clinical trials are conducted with groups of patients afflicted with a specific disease to determine preliminary evidence of efficacy, the optimal dosages, and more extensive evidence of safety. In Phase III, large scale, statistically-driven multi-center, comparative clinical trials are conducted with patients afflicted with a target disease in order to provide enough data to demonstrate the efficacy and safety required by the FDA.

The FDA requires that all pre-clinical and clinical testing, as well as manufacturing of drug product, meet certain Good Practices guidelines, including Good Manufacturing Processes, Good Laboratory Practices and Good Clinical Practices. These guidelines are designed to ensure formal training, standard operating procedures, independent performance checks and measures, the accuracy, consistency, validity and completeness of the particular activity. In our case, Contract Research Organizations, or CROs, and academic or other sponsored research laboratories that we utilize for our pre-clinical and clinical research, as well as active pharmaceutical ingredient (API) manufacturing of pure drug product, must comply with these guidelines. Our contracted manufacturers, sponsored research labs and CROs undertake to adhere to Good Manufacturing Processes, Good Laboratory Practices and Good Clinical Practices. We select only CROs that have a record of adherence to those standards and have internal quality assurance and control functions in place to ensure such adherence. However, no assurance can be given that these CROs will in fact completely adhere to the relevant standards in their work for us.

The results of all of the pre-clinical and clinical testing are submitted to the FDA in the form of a New Drug Application (NDA) for approval to commence commercial sales. In responding to an NDA, the FDA may grant marketing approval, request additional information, or deny the application if the FDA determines that the application does not satisfy its regulatory approval criteria. We cannot assure you that approvals will be granted on a timely basis, if at all. Similar regulatory procedures are in place in most developed countries outside the United States.

G. Strategic Alliances

Background: Amyloid Inhibitory Peptides (AIPs) and Prion Inhibitory Peptides (PIPs)

In AD the conversion of beta-amyloid protein into insoluble beta-sheets that aggregate to form insoluble fibrous masses (fibrils) is a key event that leads eventually to neuronal cell death in the brains of AD patients. These fibrils are deposited as part of the neurotoxic amyloid plaques that appear to cause the death of neurons in the brain. The beta-amyloid protein is a protein normally found in the brain that is over-produced in AD.

The AIPs, also referred to as beta-sheet breaker peptides, have been designed to block the aggregation of beta-amyloid in a competitive manner by binding to the beta-sheet form of the amyloid protein, thus preventing the formation of amyloid plaques in the brain. The beta-sheet breaker peptide is a molecule composed of naturally occurring amino acids, the building blocks of proteins, which is designed to bind to and prevent the conversion of the normal form of protein to the misshapen form that forms plaques.

In experiments *in vitro* and *in vivo* at labs at New York University (NYU) with one of the AIPs, the compound inhibited the formation of amyloid fibrils, caused disassembly of preformed fibrils and prevented neuronal cell death in cell culture. In a rat model of amyloidosis, an AIP reduced beta-amyloid protein deposition and significantly blocked the formation of amyloid fibrils. In addition, one of the AIPs has been shown to cause a significant reduction of established amyloid deposits in the brains of rats. These results indicate the potential for a drug based on the AIP technology to prevent the formation of the amyloid plaques, and to treat AD patients who already have amyloid plaques. Thus, the AIPs may not only prevent the formation of amyloid plaques in but also disassemble existing amyloid plaques.

There is increasing evidence that prions are the infectious agents that cause Bovine Spongiform Encephalopathy (BSE), Creutzfeldt-Jakob Disease, new variant (nvCJD) and possibly other prion-related diseases. These diseases have caused grave concern in Europe and the U.S. because of the potential for their transmission to humans through the meat supply. These fatal neurodegenerative disorders are characterized by spongiform degeneration of the brain and, in many cases, by deposits of prions into plaques. The infectivity of prions is believed to be associated with an abnormal folding of the prion protein. This folding involves a conversion of the alpha-helical form to the beta-sheet form that can be deposited in plaques in the brain.

New York University License

On April 1, 1997 we entered into a Research and License Agreement with New York University pursuant to which NYU granted us an exclusive worldwide license to certain patent applications covering AIPs, PIPs and related technology, and any inventions that arose out of the research project funded by us. Aggregate milestone payments under the agreement total $525,000, with $175,000 payable once for each of one AD treatment product, one prion treatment product and one neuro-imaging product. We must pay minimum annual royalty payments to NYU in the amount of $150,000 per year beginning in 2004, through the expiration or termination of the agreement. We also undertook to comply with a development plan annexed to the agreement, that contains deadlines by which we or our sublicensee is to achieve certain development milestones, including commencing clinical trials, for an AIP and PIP compound.

Under the Research and License Agreement, we are obligated to pay all patent filing, prosecution and maintenance costs. In addition, we paid NYU $25,000 upon signing the agreement in connection with patent expenses incurred prior to the signing of the agreement. We have the right to bring suit against any third party infringers and are responsible for all of our costs and expenses or those of NYU incurred in conjunction with such suit. If we are rewarded a recovery in our suit against a third party infringer, we may utilize such recovery to pay for our costs and expenses in bringing such action, and we must pay NYU a portion of any excess recovery over such costs and expenses. If we choose not to bring such a suit, and NYU exercises its right to do so, NYU will pay the costs and expenses of such a suit against a third party infringer. NYU has the right to reimburse itself for costs and expenses incurred in such a suit out of any sums recovered, and will pay us fifty percent of the amount of such recovery in excess of NYU s costs and expenses.

We issued an aggregate of 600,000 shares of common stock to NYU and two scientists involved in the research upon signing of the agreement. These 600,000 shares of common stock had a fair market value of $240,000 when they were issued. In addition, we granted additional shares of common stock to NYU and the two scientists pursuant to certain anti-dilution provisions relative to the shares issuance at a price of $0.001 per share. We issued an aggregate of 317,369 shares of common stock to NYU and the two scientists in 2000. We recorded accounting charges of $1,965,000 for the fair market value of 305,074 of the 317,369 shares deemed issued in 1999 and recorded accounting charges of $138,000 for the fair market value of final tranche of 12,295 shares issued in 2000 to complete the shares issuances to NYU and the two scientists.

In addition to royalties on future sales of products developed from the patented technologies, milestone payments and patent filing and prosecution costs, we undertook to fund four years of research at the NYU School of Medicine at Dr. Frangione s laboratory at a cost of $300,000 per year. That obligation ceased in the Fall of 2001, after we had paid an aggregate of $1,200,000. Under the agreement with NYU, we received an exclusive license to

all inventions in the field arising from this research on the AIPs and PIPs. We did not receive notice from NYU that any inventions in the field arose out of the research project on the AIPs and PIPs.

The patent license terminates, on a country-by-country basis, upon expiration of the last to expire of the licensed patents (June 2015 for the United States) or eight years from the date of first commercial sale of a licensed product in such country, whichever is later. Either party can terminate the Research and License Agreement if the other party materially breaches or defaults in the performance or observance of any of the provisions of the agreement and such breach or default is not cured within 60 days or, in the case of failure to pay any amounts due under the agreement, within 30 days after giving notice by the other party specifying such breach or default, or automatically and without further action if either NYU or Axonyx discontinues its business or becomes insolvent or bankrupt. Upon termination of the agreement all rights in and to the covered patent rights shall revert to NYU and we will not be entitled to impinge on such patent rights. Termination of the agreement would not relieve either party of any obligation to the other party incurred prior to such termination. Certain provisions of the Research and License Agreement will survive and remain in full force and effect after any termination, including provisions relating to confidentiality, liability and indemnification, security for indemnification, and use of name of the other party without prior written consent except under certain circumstances.

On October 11, 2002, we signed a Fourth Amendment with New York University to the Research and License Agreement between New York University and Axonyx dated April 1, 1997. The amendment modifies the development plan annexed to the Research and License Agreement regarding deadlines by which we or our sublicensee is to achieve certain development milestones, including commencing clinical trials, for an AIP compound. The amendment extends the dates by which we or our sublicensee undertakes to meet certain development and commercialization benchmarks, including the commencement of Phase I clinical trials for an AIP compound. The amendment also modifies the terms of the milestone payment provisions of the Research and License Agreement, delays the due date for the next development plan report and contains releases and waivers of default by the university and Axonyx. NYU waived any past failures on our part to develop Licensed Products in accordance with the schedule provided in the development plan under the Research and License Agreement. Axonyx had sublicensed the technology covered by the Research and License Agreement to ARS, a wholly owned subsidiary of Serono International, S.A.. We are negotiating a reacquisition of those rights from ARS. See Item 1, Business, Outlicensed Technology, Section D.

CURE, LLC, Public Health Service/National Institutes of Health

On February 27, 1997, we acquired the worldwide exclusive patent rights to Phenserine, Cymserine (a butyrylcholinesterase inhibitor), their analogs (one of a series of chemical substances of similar chemical structure) and related acetylcholinesterase and butyrylcholineserase inhibitory compounds (not including PENC or Bisnorcymserine) via a sublicense with CURE, LLC, from the Public Health Service, parent agency of the National Institutes of Health\National Institute on Aging (NIH\NIA). We have periodically sponsored some of the researchers at the NIA facilities involved in fields of research related to the licensed patent rights.

Under the license agreement, we agreed to pay royalties to CURE, LLC of up to 3% of the first $100 million and 1% thereafter, of net product sales of, and sub-licensed royalties on, products developed from the patented technologies. We also agreed to pay an upfront fee in the amount of $25,000, milestone payments aggregating $600,000 when certain clinical and regulatory milestones are reached, and patent filing and prosecution costs. We have been paying minimum annual royalty payments of $10,000 since January 31, 2000, which will increase to $25,000 per year on commencement of sales of the product until the expiration or termination of the agreement. Any royalty payments made to CURE shall be credited against the minimum payments. Four patents have been issued in the United States.

Certain pass through provisions from the License Agreement between CURE, LLC and the PHS are contained in our License Agreement with CURE, LLC and are binding on us as if we were a party to the License Agreement with the PHS. Those provisions cover certain reserved government rights to the licensed patents, preparation, filing, maintenance and prosecution of the licensed patents, obligations to meet certain benchmarks and perform a commercial development plan, manufacturing restrictions, as well as indemnification, termination and modification of rights. PHS reserves on behalf of the U.S. government or any foreign government or international organization pursuant to any existing or future treaty or agreement with the U.S. government an irrevocable, nonexclusive, nontransferable, royalty free license for the practice of all inventions licensed pursuant to the License Agreement between CURE and PHS for research or other purposes. Prior to the first commercial sale we must

provide PHS with licensed products or material for PHS use. After making the first commercial sale of licensed products until expiration of the agreement, we must use our reasonable best efforts to make the licensed products and processes reasonably accessible to the U.S. public. PHS reserves the right to terminate or modify the License Agreement if it is determined that such action is necessary to meet requirements for public use specified by federal regulations. We are also obligated, under these pass through provisions, to manufacture licensed products substantially in the U.S., unless a written waiver is obtained in advance from the PHS. We undertake to develop and commercialize any licensed products covered by the patents pursuant to a commercial development plan contained in a pass through provision from the CURE-PHS license agreement. If we fail to cure non-compliance with the commercial development plan after notice from CURE within a reasonable period of time, we could be in material breach of the agreement.

Under the pass through provisions from the License Agreement between CURE, LLC and the PHS, the PHS is primarily responsible for the preparation, filing, prosecution and maintenance of the patents covered by the License Agreement. Pursuant to our agreement with CURE, LLC, we have assumed full responsibility for the preparation, filing, prosecution and maintenance of the covered patents, and have reimbursed CURE, LLC for its patent expenses as part of the $25,000 up front fee. We have the right to pursue any actions against third parties for infringement of the patents covered by our License Agreement with CURE, LLC. Upon the conclusion of any such infringement action we may bring, we are entitled to offset unrecovered litigation expenses incurred in connection with the infringement action against a percentage of the aggregate milestone payments and royalties owed to CURE, LLC. In the event that fifty percent of such litigation expenses exceed the amount of royalties is payable by us, the expenses in excess may be carried over as a credit on the same basis into succeeding years. A credit against litigation expenses will not reduce the royalties due in any calendar year to less than the minimum annual royalty. Any recovery we make in such an infringement action shall be first applied to reimburse CURE for royalties withheld as a credit against litigation expenses and we may utilize the remainder to pay for our litigation expense. Any remaining recoveries will be shared equally by us and CURE.

The reversionary rights provision of the License Agreement sets certain deadlines by which we are to achieve certain development milestones, including commencing clinical trials, for Phenserine. If we fail to comply with the development benchmarks set forth in the reversionary rights provision, or the commercial development plan, or pay the required penalty fees, then all rights to the patents may, at CURE s election, revert to CURE, and the agreement will terminate. In addition, we have the right to terminate the agreement with 60 days notice without cause. Either party may terminate the agreement upon cause, if the other party materially breaches or defaults in the performance of any provision of the agreement and has not cured such breach or default within 90 days after notice of such breach or default, or if either party discontinues its business or becomes insolvent or bankrupt. Unless terminated first, the license terminates upon the last to expire of the licensed patents (November 2013 in Europe, extendable to November 2018 under EU Regulation (EEC) 1768/92).

On May 27, 2002, we signed an amendment letter with CURE, LLC that amends the License Agreement between Axonyx and CURE dated February 27, 1997. The amendment modifies the reversionary rights provision of the License Agreement regarding deadlines by which we are to achieve certain development milestones, including commencing clinical trials, for Phenserine. The amendment extends the dates by which reversionary rights arise if we fail to meet certain development benchmarks, including the commencement of Phase III clinical trials for Phenserine. On July 11, 2002, the Public Health Service, the parent agency of the NIH/NIA, signed an amendment to the Patent License Agreement Exclusive between the Public Health Service and CURE dated January 31, 1997, which, among other things, amends the commercial development plan and benchmark provisions of the original agreement and extends the dates by which CURE or its sublicensee Axonyx is required to commence clinical trials for Phenserine and file a New Drug Application for Phenserine. We are negotiating a further amendment of those provisions and dates.

H. Marketing and Sales

We do not intend to directly manufacture or market any products we may develop. We intend to license to, or enter into strategic alliances with, larger pharmaceutical and veterinary companies that are equipped to manufacture and/or market our products, if any, through their well developed distribution networks. We may license some or all of our worldwide patent rights to more than one company to achieve the fullest development, marketing and distribution of our products, if any.

I. Patents, Trademarks, and Copyrights

We are substantially dependent on our ability to obtain patents, proprietary rights, and operate without infringing on the proprietary rights of third parties. Our policy is to file and/or prosecute patent applications to protect technology, inventions, and improvements that we consider important to our business and operations. We or our licensors or collaborators have filed patent applications on products and processes relating to our lead compounds, Phenserine, Posiphen , and Bisnorcymserine (BNC), as well as other technologies and inventions in the United States and in certain foreign countries. We intend to file additional patent applications, when appropriate, relating to improvements in these technologies and other specific products and processes. We plan to vigorously prosecute, enforce, and defend our patents and other proprietary technology, although we recognize that the scope and validity of patents is never certain. Obtaining and maintaining our patent position is costly. We pay for the filing, prosecution and maintenance of over 150 patents and patent applications in countries around the world, including the United States, Europe, Japan, Canada, Australia, New Zealand and South Korea. In the United States alone, Axonyx has rights in ten issued patents.

In February of 1997, CURE LLC granted us an exclusive license to certain patents and patent applications relating to the development and commercialization of Phenserine. Under this license agreement we have to achieve specified benchmarks and upon receipt of marketing approval for Phenserine, to pay royalties based on the net sales. This license terminates upon expiration of the last to expire of the licensed patents (September 2011 in the United States, extendable through 2016 under the Patent Term Restoration Act of 1984).

Axonyx and the NIH jointly own rights in patent applications directed to the use of Posiphen to reduce ß-amyloid protein levels and treat the underlying pathology of AD. These patents expire in March of 2022.

Axonyx and the NIH jointly own rights in issued patents and patent applications directed to butyrylcholinesterase inhibitors, including BNC, and methods of treating cognitive disorders. These patents expire in July of 2018.

Co-ownership of a patent based on co-inventorship in the United States means that each co-inventor presumptively owns a pro-rata undivided interest in the whole patent, and has the unilateral right to exploit the patent without the consent of and without accounting to the other owners. None of the co-inventors can unilaterally grant exclusive rights to the patent to another party, nor can any co-inventor prosecute an infringement action without joining the other co-inventors. Ownership laws may vary in other countries.

Others may independently develop similar products or processes to those developed by us, and design around any products and processes covered by our patents. Defense and enforcement of our intellectual property rights can be expensive and time consuming, even if the outcome is favorable to us. It is possible that patents issued to or licensed to us will be successfully challenged, that a court may find that we are infringing validly issued patents of third parties, or that we may have to alter or discontinue the development of our products or pay licensing fees to take into account patent rights of third parties.

In April of 1997, New York University (NYU) granted us an exclusive license to certain patents and patent applications. Pursuant to an Intellectual Property Agreement, an additional patent application in this technology was assigned to us. These patents and patent applications relate to beta-breaker peptide analogs capable of inhibiting the formation of amyloid or amyloid-like deposits (AIPs and PIPs). We sublicensed this technology to a subsidiary of Serono International, S.A. See Item 1, Section D, Business, Out-licensed Technology.

We filed a U.S. trademark application for POSIPHEN filed foreign trademark applications.

We have not filed for any copyright protection to date.

J. Employees

We currently have six full time employees, two of whom are in administration, one of whom is involved in both management and research and development and three of whom are involved in management. See Item 10, Executive Compensation, for information on our employment arrangements with certain of its officers and directors.

Item 1A. Risk Factors.

Risks Related to Our Business

You should carefully consider the risks described below in evaluating Axonyx and our business. If any of the following risks actually occur, our business could be harmed. This could cause the price of our stock to decline. This Form 10K contains, in addition to historical information, forward-looking statements, including statements about future plans, objectives, and intentions that involve risks and uncertainties. Our actual results may differ materially from the results discussed in the forward-looking statements. Factors that might cause or contribute to these differences include those discussed below and elsewhere in this prospectus.

We have had clinical trial failures on our lead compound.

We have not achieved statistical significance in the primary endpoints in the Phase III trials conducted to date with our lead compound, Phenserine. We are seeking a partner to continue the development of Phenserine, including conducting additional Phase III trials. These trials are costly. We cannot assure that we will be able to successfully conclude a deal with a partner. If we do find a partner to continue developing Phenserine, we cannot assure that they will successfully develop or commercialize Phenserine.

We are a defendant in a class action lawsuit and a shareholder derivative lawsuit which, if determined adversely, could have a material adverse affect on us.

A class action securities lawsuit and a shareholder derivative lawsuit have been filed against us as described under Item 3 Legal Proceedings. We are defending against these actions vigorously; however, we do not know what the outcome of these proceedings will be and, if we do not prevail, we may be required to pay substantial damages or settlement amounts. Furthermore, regardless of the outcome, we may incur significant defense costs, and the time and attention of our management may be diverted from normal business operations. If we are ultimately required to pay significant defense costs, damages or settlement amounts, such payments could materially and adversely affect our operations and results. In any event, publicity surrounding the lawsuits and/or any outcome unfavorable to us could adversely affect our reputation and share price. The uncertainty associated with substantial unresolved lawsuits could harm our business, financial condition and reputation.

We have certain obligations to indemnify our officers and directors and to advance expenses to such officers and directors. Although we have purchased liability insurance for our directors and officers, if our insurance carriers should deny coverage, or if the indemnification costs exceed the insurance coverage, we may be forced to bear some or all of these indemnification costs directly, which could be substantial and may have an adverse effect on our business, financial condition, results of operations and cash flows. If the cost of our liability insurance increases significantly, or if this insurance becomes unavailable, we may not be able to maintain or increase our levels of insurance coverage for our directors and officers, which could make it difficult to attract or retain qualified directors and officers.

If we fail to continue to meet all applicable NASDAQ Market requirements and NASDAQ determines to delist our common stock, the delisting could adversely affect the market liquidity of our common stock and the market price of our common stock could decrease.

Our common stock is listed on the NASDAQ Capital Market (formerly known as the NASDAQ SmallCap Market). In order to maintain our listing, we must meet minimum financial and other requirements. If we are unable to comply with NASDAQ s listing standards, may determine to delist our common stock from the NASDAQ Capital Market. On December 21, 2005, we received notice from NASDAQ stating that we were out of compliance with bid price requirements because the closing bid price for our common stock was below $1.00 per share for 30 consecutive business days. On March 8, 2006 we received a letter from NASDAQ that we had regained compliance with the $1.00 per share minimum bid price requirement for continued listing on the NASDAQ Capital Market. If in the future we do not meet the NASDAQ listing requirements based on minimum bid price for our common stock, we would have 180 days to regain compliance with bid price requirements. To regain compliance the closing bid price for our common stock must be a minimum of $1.00 per share for at least 10 consecutive business days. If NASDAQ made a determination to delist our common stock, the delisting procedure would involve a process beginning with NASDAQ s notification and would include a hearing and the possibility of appeal. There is no

assurance that at the end of this process our common stock would continue to be listed on the NASDAQ Capital Market. If our common stock is delisted for any reason, it could reduce the value of our common stock and its liquidity. Delisting could also adversely affect our ability to obtain financing for the continuation of our operations or to use our common stock in acquisitions. Delisting could result in the loss of confidence by suppliers, customers and employees.

We have a limited operating history. We have a large accumulated deficit and may never become profitable.

We have a limited operating history upon which investors may base an evaluation of our likely future performance. Since we began operations in 1997 we have been engaged in developing and conducting our research and clinical programs, recruiting outside directors, employees and key consultants, evaluating potential compounds for in-licensing, and consummating patent licensing agreements. To date, we have not had any in-house laboratory facilities in which to conduct any research and will not have any operational laboratories of our own in the near future. We have had only limited revenue from license fees in the amount of $2.75 million to date. As of December 31, 2005, we had an accumulated deficit of $91,122,000 and our operating losses are continuing.

We have no products available for sale and we may never be successful in developing products suitable for commercialization.

With the exception of Phenserine, all of our drug candidates are at an early stage of development and all of our drug candidates will require expensive and lengthy testing and regulatory clearances. None of our drug candidates have been approved by regulatory authorities. We have no products available for sale and we do not expect to have any products commercially available for several years, if at all. There are many reasons that we may fail in our efforts to develop our drug candidates, including that:

Our drug candidates will be ineffective, toxic or will not receive regulatory clearances,

Our drug candidates will be too expensive to manufacture or market or will not achieve broad market acceptance,

Our candidates may face generic competition by the time they reach the market place and therefore preclude a return on our investment,