
UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

**Amendment No. 4 to
Form S-1**
**REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

Targacept, Inc.

(Exact name of registrant as specified in its charter)

Delaware
*(State or other jurisdiction
of incorporation or organization)*

2834
*(Primary Standard Industrial
Classification Code Number)*
**200 East First Street, Suite 300
Winston-Salem, North Carolina 27101
(336) 480-2100**

56-2020050
*(I.R.S. Employer
Identification Number)*

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

J. Donald deBethizy
Chief Executive Officer
Targacept, Inc.
**200 East First Street, Suite 300
Winston-Salem, North Carolina 27101
(336) 480-2100**

*(Name, address, including zip code, and telephone number,
including area code, of agent for service)*

Copies to:

Jonathan L. Kravetz, Esq.
Megan N. Gates, Esq.
**Mintz, Levin, Cohn, Ferris,
Glovsky and Popeo, P.C.**
One Financial Center
Boston, Massachusetts 02111
(617) 542-6000

Jeffrey C. Howland, Esq.
Womble Carlyle
Sandridge & Rice, PLLC
One West Fourth Street
Winston-Salem,
North Carolina 27101
(336) 721-3516

Peter A. Zorn, Esq.
Targacept, Inc.
200 East First Street,
Suite 300
Winston-Salem,
North Carolina 27101
(336) 480-2115

David E. Redlick, Esq.
Stuart R. Nayman, Esq.
Wilmer Cutler Pickering
Hale and Dorr LLP
399 Park Avenue
New York, New York 10022
(212) 937-7200

Approximate date of commencement of proposed sale of the securities to the public: As soon as practicable after the effective date of this Registration Statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended (the "Securities Act"), check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. _____

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier registration statement for the same offering. _____

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier registration statement for the same offering. _____

If delivery of the Prospectus is expected to be made pursuant to Rule 434, please check the following box.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is declared effective. This preliminary prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to Completion, Dated January 20, 2005



Common Stock

This is the initial public offering of Targacept, Inc. We are offering _____ shares of our common stock. We anticipate that the initial public offering price will be between \$ _____ and \$ _____ per share. We have applied to list our common stock on the Nasdaq National Market under the symbol "TRGT."

Investing in our common stock involves risk. See "[Risk Factors](#)" beginning on page 7.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

| | Price to Public | Underwriting Discounts and Commissions | Proceeds to Targacept |
|-----------|-----------------|--|-----------------------|
| Per Share | \$ _____ | \$ _____ | \$ _____ |
| Total | \$ _____ | \$ _____ | \$ _____ |

We have granted the underwriters the right to purchase up to _____ additional shares of common stock to cover over-allotments.

Deutsche Bank Securities

Pacific Growth Equities, LLC

CIBC World Markets

Lazard

The date of this prospectus is _____, 2005

PROSPECTUS SUMMARY

The following summary highlights information appearing elsewhere in this prospectus. It may not contain all of the information that may be important to you in deciding whether to invest in our common stock. You should read the entire prospectus carefully, including the "Risk Factors" section and the financial statements and related notes appearing at the end of this prospectus, before making an investment decision.

TARGACEPT, INC.

We are a biopharmaceutical company engaged in the design, discovery and development of a new class of drugs to treat multiple diseases and disorders of the central nervous system by selectively targeting neuronal nicotinic acetylcholine receptors, or NNRs. NNRs are found on nerve cells throughout the nervous system and serve as key regulators of nervous system activity. Our product candidates are designed to selectively target specific NNR subtypes to promote positive medical effects and limit or potentially eliminate adverse side effects.

We are developing our most advanced product candidates as treatments for target indications in three therapeutic areas: cognitive impairment, pain and depression. Within these areas, we have three product candidates in clinical development and three preclinical product candidates. We expect to advance one of our preclinical product candidates into clinical development in the first half of 2005. We also have multiple preclinical programs for target indications outside these areas in which we believe that NNRs can be exploited for medical benefit. We have worldwide commercialization rights for all of our product candidates. Our most advanced product candidates are:

Cognitive Impairment

- **Ispronicline (TC-1734).** Ispronicline is a novel small molecule that we are developing as an oral treatment for conditions marked by cognitive impairment that afflict the elderly, including Alzheimer's disease and age associated memory impairment, commonly referred to as AAMI. In 2004, we completed two Phase II clinical trials of ispronicline, one in AAMI and one in mild cognitive impairment, commonly referred to as MCI. We began screening subjects for a separate Phase II clinical trial of ispronicline in AAMI in the fourth quarter of 2004. We plan to initiate two Phase II clinical trials of ispronicline in Alzheimer's disease in 2005. We expect the first of these trials, which we plan to initiate in mid-2005, to assess ispronicline as a stand-alone treatment for mild Alzheimer's disease. We expect the second of these trials, which we plan to initiate in the second half of 2005, to assess ispronicline as a complementary, or add-on, therapy to a currently approved treatment for mild to moderate Alzheimer's disease. We are also evaluating potential additional clinical development of ispronicline for indications such as cognitive impairment associated with schizophrenia, cognitive impairment following coronary artery bypass grafting, MCI, attention deficit hyperactivity disorder and various forms of dementia.
- **TC-1827.** TC-1827 is a novel small molecule that we are developing as an oral treatment for cognitive impairment associated with schizophrenia under a development agreement that we entered into in December 2004 with The Stanley Medical Research Institute. TC-1827 is currently a preclinical product candidate. We plan to file an investigational new drug application, or IND, and initiate a Phase I clinical trial of TC-1827 in the first half of 2005.

Pain

- **TC-2696.** TC-2696 is a novel small molecule that we are developing as an oral treatment for acute post-operative pain. Depending on clinical trial results, available resources and other considerations, we may pursue development of TC-2696 for other classes of pain as well. In 2004, we completed a Phase I clinical trial of TC-2696. We plan to initiate a Phase I multiple rising dose clinical trial to further assess the safety and tolerability profile of TC-2696 in the second quarter of 2005. If the results of that trial are favorable, we plan to initiate a Phase II clinical trial of TC-2696 in hysterectomy or molar extraction patients in the first half of 2006.

Depression

- ***Inversine and TC-5214.*** We began screening patients for a Phase II clinical trial of our product Inversine as an add-on therapy in patients with major depressive disorder in January 2005. Inversine, which we believe is the only FDA-approved product designed to target an NNR, is approved in the United States for the management of moderately severe to severe essential hypertension, a high blood pressure disorder with an unknown origin. However, we believe that Inversine is prescribed predominantly for the treatment of neuropsychiatric disorders, including Tourette's syndrome, autism and bipolar disorder, in children and adolescents at a lower dose than is used to treat hypertension. TC-5214 is one of the molecular components of mecamlamine hydrochloride, the active ingredient in Inversine. TC-5214 is currently a preclinical product candidate. We are evaluating the development of TC-5214 as an add-on therapy for depression.
- ***TC-2216.*** TC-2216 is a novel small molecule that we are developing as an oral treatment for depression and anxiety disorders. TC-2216 is currently a preclinical product candidate. In 2005, we plan to conduct the additional preclinical toxicology studies necessary to support an IND for clinical trials of TC-2216.

In addition, we have preclinical research programs in schizophrenia, smoking cessation and obesity.

We trace our scientific lineage to a research program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and effects of nicotine, a compound that interacts non-selectively with all nicotinic acetylcholine receptors. There is a significant amount of published clinical data relating to nicotine, including studies in which individuals with Alzheimer's disease and other conditions marked by cognitive impairment showed therapeutic improvement when treated with a nicotine patch. We have used this clinical data, together with our deep understanding of the biological characteristics and functions of NNRs that we have built over more than 20 years, to validate NNRs as potential targets for drugs to act upon. We have also developed an expertise in designing compounds of low molecular weight, referred to as small molecules, that can selectively interact with specific NNR subtypes, with the objective of eliciting a desired effect and limiting or potentially eliminating side effects such as those typically seen with nicotine. We have built an extensive patent estate covering the structure or therapeutic use of small molecules designed to regulate the central nervous system by selectively affecting specific NNR subtypes.

We develop product candidates using our proprietary databases and computer-based molecular design technologies, which we refer to collectively as Pentad. Together with our proprietary assays and novel screening methods, Pentad enables us to efficiently identify, prioritize, characterize and optimize novel compounds. We used Pentad to design or optimize ispronicline, TC-1827, TC-2696 and TC-2216.

Our Business Strategy

Our goal is to become a leader in the discovery, development and commercialization of novel drugs that selectively target NNRs in order to treat diseases and disorders where there is significant medical need and commercial potential. To achieve this goal, we are pursuing the following strategies:

- ***Develop and commercialize drugs that selectively target specific NNR subtypes.*** Based on our understanding of the role of NNRs in the nervous system, we believe that drugs designed to selectively target specific NNR subtypes can have positive medical effects with limited or no adverse side effects.
- ***Remain at the forefront of the commercialization of NNR research.*** We have established ourselves as a leader in NNR research over the last 20 years. We intend to continue to invest significant resources to build upon our NNR expertise and to expand our intellectual property portfolio.
- ***Identify and prioritize indications in which drugs that selectively target specific NNR subtypes can be exploited for medical benefit.*** We have identified numerous indications in which NNRs have been implicated and for which we believe drugs that selectively target specific NNR subtypes can provide a medical benefit. We prioritize our product development in an effort to sustain our product pipeline.

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- *Collaborate selectively to develop and commercialize product candidates.* We intend to selectively enter into collaboration agreements with leading pharmaceutical and biotechnology companies to assist us in furthering the development of our product candidates. In entering into these collaboration agreements, our goal will be to maintain co-promotion or co-commercialization rights in the United States and, in some cases, other markets.
- *Build a specialized sales and marketing organization.* We intend to build an internal sales and marketing organization for target indications in which specialists heavily influence the market, particularly neurology and psychiatry. We believe that we can effectively serve these markets with a specialized sales force, enabling us to retain greater value from our product candidates that receive marketing approval than if we relied on a third party's sales force.

Risks Associated with Our Business

Our business is subject to numerous risks, as more fully described in the section entitled "Risk Factors" immediately following this prospectus summary. We have a limited operating history and have incurred substantial net losses since our incorporation in 1997. We expect to continue to incur substantial losses for the foreseeable future. Inversine is the only product that we have available for commercial sale, and it generates limited revenues. All of our other product candidates are undergoing clinical trials or are in early stages of development, and failure is common and can occur at any stage of development. None of our product candidates, other than Inversine, has received regulatory approval for marketing and sale. Our ability to generate product revenue in the future will depend heavily on the successful development and commercialization of these product candidates. Even if we succeed in developing and commercializing one or more of our product candidates, we may never generate sufficient sales revenue to achieve and then sustain profitability.

Company History

Our history traces back to 1982 when R.J. Reynolds Tobacco Company initiated a program to study the activity and effects of nicotine in the body. We were incorporated in Delaware in 1997 as a wholly owned subsidiary of RJR and became an independent company in August 2000. Our executive offices are located at 200 East First Street, Suite 300, Winston-Salem, North Carolina 27101, and our telephone number is (336) 480-2100. Our web site is located at www.targacept.com. Information contained on our web site is not incorporated by reference into, and does not form any part of, this prospectus. We have included our website address in this document as an inactive textual reference only. Our trademarks include Targacept® and Inversine®. Other service marks, trademarks and trade names appearing in this prospectus are the property of their respective owners. Unless the context requires otherwise, references in this prospectus to the "company," "we," "us," and "our" refer to Targacept, Inc.

THE OFFERING

| | |
|--|---|
| Common stock offered by Targacept | shares |
| Common stock to be outstanding after this offering | shares |
| Over-allotment option | shares |
| Use of proceeds | To fund clinical trials, preclinical testing and other research and development activities, manufacturing expenses, general and administrative expenses, working capital needs and other general corporate purposes. See "Use of Proceeds." |
| Risk factors | You should read the "Risk Factors" section of this prospectus for a discussion of the factors to consider carefully before deciding to invest in shares of our common stock. |
| Proposed NASDAQ National Market symbol | TRGT |

The number of shares of our common stock that will be outstanding immediately after this offering is based on _____ shares outstanding as of _____, 2005, and includes:

- 103,204,189 shares of common stock issuable upon the conversion of all currently outstanding shares of our series A, series B and series C convertible preferred stock concurrently with the completion of this offering;
- _____ shares of common stock issuable upon the conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share; and
- _____ shares of common stock issuable upon the exercise of an outstanding warrant that will expire if not exercised concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share. The cash exercise price of the warrant is \$ _____ per share.

The number of shares of our common stock that will be outstanding immediately after this offering excludes:

- 7,408,736 shares of common stock issuable upon the exercise of options outstanding as of December 31, 2004, at a weighted average exercise price of \$0.65 per share, of which options to purchase 4,400,303 shares were exercisable; and
- 302,143 shares of common stock reserved for future grant under our 2000 equity incentive plan as of December 31, 2004.

Unless otherwise indicated, all information in this prospectus assumes:

- no exercise by the underwriters of their over-allotment option to purchase up to _____ shares of our common stock;
- the conversion of all outstanding shares of our convertible preferred stock into 103,204,189 shares of common stock concurrently with the completion of this offering;
- the issuance of _____ shares of common stock upon the conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share; and
- the issuance of _____ shares of common stock upon the exercise of an outstanding warrant that will expire if not exercised concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share.

In addition, unless otherwise noted, all information in this prospectus gives effect to the one-for-_____ reverse stock split of our common stock that will be effective prior to the completion of this offering.

SUMMARY FINANCIAL DATA

The following tables summarize our financial data. You should read the following summary financial data together with our financial statements and the related notes appearing at the end of this prospectus and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section and other financial information included in this prospectus.

The pro forma net loss attributable to common stockholders per share information is computed using the weighted average number of common shares outstanding, after giving pro forma effect to the conversion of all shares of our convertible preferred stock outstanding as of December 31, 2003 and September 30, 2004 into 73,739,905 shares of common stock concurrently with the completion of this offering, as if the conversion had occurred at the date of the original issuance. This pro forma information does not give effect to the issuance of additional shares of our convertible preferred stock on December 6, 2004, to the conversion of an outstanding convertible promissory note or to the exercise of an outstanding warrant.

| | Year ended December 31, | | | Nine months ended September 30, | |
|---|---|--------------------|--------------------|------------------------------------|-------------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| | (in thousands, except share and per share data) | | | | |
| | (unaudited) | | | | |
| Statement of Operations Data: | | | | | |
| Net revenue | \$ 1,703 | \$ 2,286 | \$ 2,458 | \$ 1,816 | \$ 1,581 |
| Operating expenses: | | | | | |
| Research and development | 8,152 | 16,244 | 18,179 | 13,376 | 17,782 |
| General and administrative | 2,302 | 4,135 | 3,600 | 2,698 | 3,764 |
| Cost of product sales | — | 244 | 743 | 540 | 28 |
| Purchased in-process research and development | — | 2,666 | — | | |
| Total operating expenses | 10,454 | 23,289 | 22,522 | 16,614 | 21,574 |
| Loss from operations | (8,751) | (21,003) | (20,064) | (14,798) | (19,993) |
| Interest and dividend income | 1,449 | 88 | 791 | 546 | 356 |
| Interest expense | — | (103) | (122) | (96) | (96) |
| Loss on disposal of fixed assets | — | (54) | — | | (4) |
| Net loss | (7,302) | (21,072) | (19,395) | (14,348) | (19,737) |
| Preferred stock accretion | (3,808) | (4,173) | (8,341) | (6,199) | (6,426) |
| Net loss attributable to common stockholders | \$ (11,110) | \$ (25,245) | \$ (27,736) | (20,547) | (26,163) |
| Basic and diluted net loss per share applicable to common stockholders | \$ (26.80) | \$ (45.28) | \$ (33.91) | \$ (27.04) | \$ (16.82) |
| Shares used to compute basic and diluted net loss per share | 414,624 | 557,492 | 817,894 | 759,937 | 1,555,090 |
| Pro forma basic and diluted net loss per share applicable to common stockholders (unaudited) | | | \$ (0.27) | | \$ (0.26) |
| Shares used to compute pro forma basic and diluted net loss per share (unaudited) | | | 71,118,629 | | 75,294,995 |

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The pro forma balance sheet information gives effect to the issuance of additional shares of our convertible preferred stock on December 6, 2004, the issuance of a convertible promissory note on December 15, 2004 and the conversion of all outstanding shares of our convertible preferred stock into 103,204,189 shares of common stock concurrently with the completion of this offering. The pro forma as adjusted balance sheet information gives further effect to:

- our sale of _____ shares of common stock in this offering at an assumed initial public offering price of \$ _____ per share, after deducting estimated underwriting discounts and commissions and offering expenses payable by us;
- our issuance of _____ shares of common stock upon the conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial offering price of \$ _____ per share; and
- our issuance of _____ shares of common stock upon the exercise of an outstanding warrant that will expire if not exercised concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share. The cash exercise price of the warrant is \$ _____ per share.

As of September 30, 2004

| | <u>Actual</u> | <u>Pro Forma</u> | <u>Pro Forma</u> |
|---|---------------|------------------|------------------|
| | | (unaudited) | As Adjusted |
| | | (in thousands) | |
| Balance Sheet Data: | | | |
| Cash, cash equivalents and short-term investments | \$ 24,425 | \$ 58,575 | |
| Working capital | 21,054 | 55,204 | |
| Total assets | 29,208 | 63,358 | |
| Long-term debt, net of current portion | 1,654 | 2,904 | |
| Redeemable convertible preferred stock | 136,560 | — | |
| Accumulated deficit | (117,835) | (117,835) | |
| Total stockholders' equity (deficit) | (116,394) | 53,066 | |

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this prospectus before deciding to invest in our common stock. If any of these risks actually occurs, our business, business prospects, financial condition, results of operations or cash flows would likely suffer, maybe materially. This could cause the trading price of our common stock to decline, and you could lose part or all of your investment.

Risks Related to Our Financial Results and Need for Additional Financing

We have incurred losses since our inception and anticipate that we will continue to incur substantial losses for the foreseeable future. We may never achieve or sustain profitability.

We were incorporated in 1997 and operated as a wholly owned subsidiary of R.J. Reynolds Tobacco Company until August 2000. We have a limited operating history and have incurred substantial net losses since our inception. As of September 30, 2004, we had an accumulated deficit of \$117.8 million. Our net loss was \$19.7 million for the nine months ended September 30, 2004, \$19.4 million for the year ended December 31, 2003 and \$21.1 million for the year ended December 31, 2002. Our losses have resulted principally from costs incurred in connection with our research and development activities, including clinical trials, and from general and administrative expenses associated with our operations. We expect to continue to incur substantial losses for the foreseeable future. We expect our research and development expenses to increase substantially following completion of this offering as we expand our clinical trial activity and as our product candidates advance through the development cycle. We also expect our general and administrative costs to increase substantially as we expand our infrastructure. As a result, we will need to generate significant revenues to pay these costs and achieve profitability.

Inversine is our only current source of product revenue. We acquired the rights to Inversine in August 2002. Sales of Inversine generated revenues of only \$584,000 for the nine months ended September 30, 2004 and \$815,000 for the year ended December 31, 2003. Inversine is approved in the United States for the treatment of moderately severe to severe essential hypertension, a high blood pressure disorder with an unknown origin. However, we believe that the substantial majority of Inversine sales are derived from prescriptions written by a very limited number of physicians for the treatment of neuropsychiatric disorders, including Tourette's syndrome, autism and bipolar disorder, in children and adolescents. If any of these physicians were to change their prescribing habits, Inversine sales would suffer. We do not expect that sales of Inversine will increase substantially in the future.

If we are unable to develop and commercialize any of our product candidates, if development is delayed or if sales revenue from any product candidate that receives marketing approval is insufficient, we may never become profitable. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

We will require substantial additional financing and our failure to obtain additional funding when needed could force us to delay, reduce or eliminate our product development programs or commercialization efforts.

We will require substantial future capital in order to continue to conduct the research and development and clinical and regulatory activities necessary to bring our product candidates to market and to establish marketing and sales capabilities. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and cost of preclinical development and laboratory testing and clinical trials;
- the costs, timing and outcomes of regulatory reviews;
- the number and characteristics of product candidates that we pursue;

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- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims;
- the costs of establishing sales and marketing functions and of establishing arrangements for manufacturing;
- the rate of technological advancements for the indications that we target;
- our ability to establish strategic collaborations and licensing or other arrangements on terms favorable to us;
- the costs to satisfy our obligations under existing and potential future collaborations;
- the timing, receipt and amount of sales or royalties, if any, from our potential products; and
- the extent and scope of our general and administrative expenses.

In addition, we may seek additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates or grant licenses on terms that are not favorable to us.

Our current operating plan provides for us to continue, either alone or with a collaborator, to advance our product candidates through the development process. It is also our objective to continue to invest in our preclinical programs and to file at least one investigational new drug application, or IND, or foreign equivalent each year beginning in 2005. We do not expect our existing capital resources and the net proceeds from this offering to be sufficient to enable us to fund the completion of the development of any of our product candidates. We expect that our existing capital resources and the net proceeds from this offering will enable us to maintain currently planned operations through the end of 2006. However, our operating plan may change as a result of many factors including those described above, and we may need additional funds sooner than planned to meet operational needs and capital requirements for product development and commercialization. Other than a modest amount of committed equipment financing, we currently have no credit facility or committed sources of capital. Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available on a timely basis, we may:

- terminate or delay clinical trials for one or more of our product candidates;
- delay our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates; or
- curtail significant drug development programs that are designed to identify new product candidates.

Risks Related to the Development and Regulatory Approval of Our Product Candidates

Our success depends substantially on our most advanced product candidates, which are still under development. If we are unable to bring any or all of these product candidates to market, or experience significant delays in doing so, our ability to generate product revenue and our likelihood of success will be harmed.

Inversine is our only marketed product and generates limited revenues. We are currently screening patients for a Phase II clinical trial of Inversine as an add-on therapy in patients with major depressive disorder. Other than Inversine, ispronidine is our only product candidate currently in a Phase II clinical trial, and we have not yet commenced clinical trials of ispronidine for the treatment of Alzheimer's disease. Although we have completed one Phase I clinical trial for TC-2696, our product candidate for the treatment of pain, we plan to conduct an additional Phase I clinical trial for TC-2696. We have not conducted any clinical trials for TC-1827, our product candidate for the treatment of cognitive impairment associated with schizophrenia. Our ability to generate product revenue in the future will depend heavily on the successful development and commercialization of

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ispronicline, TC-2696 and TC-1827. Our other product candidates are in various stages of preclinical development. Any of our product candidates could be unsuccessful if it:

- does not demonstrate acceptable safety and efficacy in preclinical studies or clinical trials or otherwise does not meet applicable regulatory standards for approval;
- does not offer therapeutic or other improvements over existing or future drugs used to treat the same conditions;
- is not capable of being produced in commercial quantities at acceptable costs; or
- is not accepted in the medical community and by third-party payors.

We do not expect any of our current product candidates to be commercially available for at least five years, if at all. If we are unable to make our product candidates commercially available, we will not generate substantial product revenues and we will not be successful.

If we do not obtain the regulatory approvals required to market and sell our product candidates, our ability to generate product revenue will be materially impaired and our business will not be successful.

The preclinical laboratory testing, development, manufacturing and clinical trials of product candidates that we develop, whether independently or in collaboration with a third party, as well as their distribution, sale and marketing, are regulated by the FDA and other federal, state and local governmental authorities in the United States and by similar agencies in other countries. We must receive regulatory approval of each product candidate before we can market and sell it. We have only limited experience in pursuing regulatory approvals. Securing FDA approval requires the submission of extensive preclinical and clinical data and information about the chemistry and manufacture of, and control procedures for, each potential product. In addition, the supporting information submitted to the FDA for each indicated use must establish the safety and efficacy of the product candidate. The marketing approval process takes many years, requires the expenditure of substantial resources, is subject to delays and can vary substantially based upon the type, complexity and novelty of the product candidates involved. In addition to the time and expense involved, the process is uncertain and we may never receive the required regulatory approvals. In addition, the FDA, the U.S. Congress and foreign regulatory authorities may from time to time change approval policies or adopt new laws or regulations, either of which could prevent or delay our receipt of required approvals. Even if we receive regulatory approval to market a particular product candidate, the approval will be subject to limitations on the indicated uses for which it may be marketed and may not permit labeling claims that are necessary or desirable for its promotion.

According to the FDA, a Phase I clinical trial program typically takes several months to complete, a Phase II clinical trial program typically takes several months to two years to complete and a Phase III clinical trial program typically takes one to four years to complete. Industry sources report that the preparation and submission of a new drug application, or NDA, which is required for regulatory approval in the United States, generally takes six months to one year to complete after completion of a pivotal clinical trial. Industry sources also report that approximately 10% to 15% of all NDAs accepted for filing by the FDA are not approved and that FDA approval, if granted, usually takes approximately one year after submission, although it may take longer if additional information is required by the FDA. In addition, the Pharmaceutical Research and Manufacturers of America reports that only one out of five product candidates that enter clinical trials will ultimately be approved by the FDA for commercial sale.

The FDA may delay, limit or deny approval of any of our product candidates for many reasons. For example:

- clinical trial results may indicate that the product candidate is not safe or effective;
- the FDA may interpret our clinical trial results to indicate that the product candidate is not safe or effective, even if we interpret the results differently;
or

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- the FDA may deem the processes and facilities that we, our collaborative partners or our third-party manufacturers propose to use in connection with the manufacture of the product candidate to be unacceptable.

In particular, because drugs that target NNRs are a new class of drugs, the FDA and other applicable regulatory authorities may require more preclinical or clinical data for our product candidates or more time to evaluate that data than we currently anticipate. If we obtain the requisite regulatory approval for a particular product candidate, the approval may not extend to all indications for which we have sought approval, which could limit the use of the product and adversely impact our potential revenues.

Even if the FDA approves a product candidate for marketing and sale in the United States, applicable regulatory authorities in other countries may not approve the product candidate or may subject their approval to conditions such as additional product testing or otherwise cause delays. The regulatory approval process varies among countries, but generally includes all of the risks associated with obtaining FDA approval. In addition, many countries require a separate review process prior to marketing to determine whether their respective national health insurance schemes will pay for newly approved products, as well as the price that may be charged for a product. This process will cause delays in the marketing of any of our product candidates that receives marketing approval and could adversely impact our revenues and results of operations.

If clinical trials for our product candidates are not successful, we will not obtain the regulatory approvals required to market and sell them.

To obtain the requisite regulatory approvals to market and sell any of our product candidates, we must demonstrate, through extensive preclinical studies and clinical trials, that the product candidate is safe and effective in humans. The number of clinical trials required to obtain approval varies depending on the particular product candidate, the disease or condition for which it is in development and the regulations applicable to it. Preclinical studies and clinical trials are lengthy and expensive, difficult to design and implement and subject to a historically high rate of failure. The development of each of our product candidates involves significant risks at each stage of testing. A failure of one or more of our clinical trials could occur at any stage of testing. In particular, we completed Phase II clinical trials in 2004 for two product candidates that we had been developing, one for attention deficit hyperactivity disorder and one for ulcerative colitis. Because we determined that these product candidates failed to meet defined endpoints of the Phase II clinical trials, we discontinued the development of these product candidates. If we experience similar difficulties or failures in our ongoing or future clinical trials, or if we are not able to design our clinical trials with clear criteria to determine the efficacy of our product candidates, our product candidates may never be approved for sale or become commercially available.

We may not be able to obtain authority from the FDA, other applicable regulatory authorities or the institutional review boards at our intended investigational sites to commence or complete our clinical trials. Before a clinical trial may commence in the United States, we must submit an IND containing preclinical studies, chemistry, manufacturing, control and other information and a study protocol to the FDA. If the FDA does not object within 30 days after submission of the IND, then the trial may commence. If commenced, we, the FDA, other applicable regulatory authorities or institutional review boards may delay, suspend or terminate clinical trials of a product candidate at any time if, among other reasons, we or they believe the subjects or patients participating in the clinical trials are being exposed to unacceptable health risks or for other reasons.

If we do not prove in clinical trials that our product candidates are safe and effective, we will not obtain marketing approvals from the FDA and other applicable regulatory authorities. In particular, one or more of our product candidates may not exhibit the expected medical benefits in humans, may cause harmful side effects or may have other unexpected characteristics that preclude regulatory approval for any or all indications of use or limit commercial use if approved.

In particular, we are developing ispronicline both as a stand-alone treatment for mild Alzheimer's disease and as an add-on therapy for mild to moderate Alzheimer's disease. To assess ispronicline as an add-on therapy, we plan to conduct a Phase II clinical trial of ispronicline together with a currently approved treatment for mild to moderate Alzheimer's disease in patients who have been taking the approved treatment for an extended period

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of time. It is possible that some or all of the patients who participate in this trial will, prior to their participation, have already derived the maximum medical benefit possible for them as a result of their extended use of the currently approved treatment. In that event, ispronicline may appear not to be effective as an add-on therapy because these patients will not be capable of deriving any additional medical benefit from further treatment. As a result, it may be particularly difficult for us to demonstrate in clinical trials that ispronicline is effective as an add-on therapy. If we are unable to demonstrate that ispronicline is effective as an add-on therapy in Alzheimer's disease patients who are taking other medication, the FDA or foreign regulatory authorities may not grant us approval to market ispronicline as an add-on therapy for mild to moderate Alzheimer's disease.

In addition, we are also developing ispronicline as a treatment for age associated memory impairment, commonly referred to as AAMI. AAMI is a condition that is characterized by gradual memory loss or other cognitive impairment that generally occurs with normal aging. Because AAMI accompanies normal aging, is not a disease state and does not prevent a person from functioning on a daily basis, the FDA or foreign regulatory authorities may require that we establish that ispronicline meets a higher threshold of safety than the FDA or foreign regulatory authorities would require for diseases and more severe disorders. If we are unable to demonstrate that ispronicline meets this higher safety threshold, the FDA or foreign regulatory authorities may not grant us approval to market ispronicline for the treatment of AAMI.

Our research and preclinical programs and product candidates target diseases or disorders that are not well understood. For example, there is only limited scientific understanding of the causes of Alzheimer's disease, AAMI, schizophrenia, including cognitive impairment associated with schizophrenia, and depression and anxiety. In addition, there are no approved drugs that target NNRs to treat these diseases, and there is only limited scientific understanding of the relationships between these diseases and the neurological pathways targeted by our product candidates and research and preclinical programs. These uncertainties increase the risk that one or more of our clinical trials will not be successful.

If success in preclinical studies or early clinical trials of our product candidates does not continue in later clinical trials, we will not obtain the regulatory approvals required to market and sell our product candidates.

Positive findings in preclinical studies of a product candidate may not be predictive of similar results in clinical trials in humans. In addition, successful results in early clinical trials of a product candidate may not be replicated in later clinical trials. In particular, we have completed Phase II clinical trials of ispronicline in AAMI and mild cognitive impairment, commonly referred to as MCI. In these trials, ispronicline demonstrated positive effects on cognition. However, because we designed the size and duration of dosing of our completed Phase II AAMI and MCI trials primarily to evaluate the safety of ispronicline, our findings in those trials on cognition may not be replicated in our ongoing Phase II AAMI trial or in future clinical trials of ispronicline that are designed primarily to evaluate efficacy and involve a large number of subjects and a long duration of dosing.

In addition, like most drugs, the active component of ispronicline must be combined with an inactive component to form a powder, known as a salt, that is suitable for commercialization as a pharmaceutical product. We are developing a salt form of ispronicline that is different from the salt form of ispronicline that we used in our completed trials, that we are currently using in our ongoing Phase II trial in AAMI and that we plan to use in our Phase II trial in mild Alzheimer's disease. We anticipate that we will use the new salt form in our planned Phase II trial of ispronicline as an add-on therapy for Alzheimer's disease and in future clinical trials of ispronicline. The results of our completed clinical trials of ispronicline may not be replicated in our planned Phase II clinical trial of ispronicline as an add-on therapy for Alzheimer's disease or any future clinical trial if we use a different salt form of the product candidate in that Alzheimer's disease trial or any future clinical trial.

In our completed clinical trials of ispronicline in AAMI and MCI, we used a battery of tests developed by CDR Ltd. to assess each subject's cognitive function. We are also using the CDR test battery in our ongoing Phase II clinical trial of ispronicline in AAMI and plan to use the CDR test battery in any future clinical trials of

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ispronicline in AAMI. However, if we change our plans and use an additional or a different test battery for future AAMI trials, there would be a greater risk that the results of our completed Phase I and Phase II clinical trials of ispronicline will not be replicated in those future clinical trials.

If we do not have success in our clinical trials of ispronicline for Alzheimer's disease, we will not obtain the regulatory approvals required to market ispronicline for Alzheimer's disease notwithstanding positive results in completed or future clinical trials of ispronicline in other indications.

We are developing ispronicline for conditions marked by various degrees of cognitive impairment in the elderly. Successful results in clinical trials of ispronicline in a condition marked by one degree of cognitive impairment may not be predictive of successful results in clinical trials of ispronicline in a condition marked by more severe cognitive impairment. In particular, we have not yet conducted any clinical trials of ispronicline in Alzheimer's disease. Our findings in our completed Phase II trials of ispronicline in persons with AAMI or MCI may not be predictive of the effect of ispronicline on cognitive impairment in Alzheimer's disease patients.

The CDR test battery that we used in our completed clinical trials of ispronicline is different from the Alzheimer's Disease Assessment Scale-cognitive subscale, or ADAS-Cog, the test battery that is most often used to assess the efficacy of drugs for Alzheimer's disease. ADAS-Cog is designed to measure improvement in persons who are severely impaired and is generally less sensitive than the CDR test battery in measuring improvement in persons who are less impaired. We plan to use ADAS-Cog, and not the CDR test battery, as a primary endpoint in our clinical trials of ispronicline in Alzheimer's disease. Our findings in our completed trials as to the effect of ispronicline on various aspects of cognition as measured by the CDR test battery may not be predictive of the effect of ispronicline on cognition as measured by ADAS-Cog. If our future clinical trials of ispronicline in Alzheimer's disease are not successful, we will not obtain the regulatory approvals required to market ispronicline for Alzheimer's disease.

If the FDA or foreign regulatory authorities do not consider AAMI to be a clinical indication appropriate for the approval of a drug, we will not receive the regulatory approvals required to market and sell ispronicline for AAMI.

We are developing ispronicline for conditions marked by cognitive impairment that afflict the elderly, including Alzheimer's disease and AAMI. Neither the FDA nor, to our knowledge, any foreign regulatory authority has approved a drug indicated for use in the treatment of AAMI. Furthermore, AAMI is not listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, or DSM-IV, the manual published by the American Psychiatric Association to establish diagnostic criteria. We do not know if the FDA or any foreign regulatory authority will be willing to recognize AAMI as a distinct clinical condition, or in the FDA's terminology, a clinical entity, for which approval of a drug is possible. If neither the FDA nor any foreign regulatory authority recognizes AAMI as a clinical entity, we will not obtain the regulatory approval required to market ispronicline for AAMI even if our clinical trials show that ispronicline is safe and provides a medical benefit for the persons treated.

When the FDA assesses whether a proposed clinical entity justifies labeling, it generally requires that the existence of the clinical entity be broadly accepted by medical experts in the relevant clinical discipline and that the clinical entity can be defined in practice. This means that the clinical entity must be able to be diagnosed using valid and reliable criteria that are widely accepted by those medical experts. The FDA imposes these requirements to assure that both the population for whom a drug is intended and the effects of the drug in that population can be adequately described in labeling for the drug. The FDA has informed us that it believes it is questionable whether AAMI satisfies these criteria. In a recent letter that we received from the FDA in response to our submission of the protocol for our ongoing Phase II trial of ispronicline for the treatment of AAMI, the FDA advised us that, in its view, because varying methodologies and criteria have historically been used by medical experts to define AAMI, the requisite consensus in the medical community has not been established. As a result, the FDA has informed us that it is unclear whether our Phase II clinical trial design and efficacy

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endpoints will measure the clinical effects appropriate for a treatment for AAMI. If we are unable to establish to the satisfaction of the FDA or foreign regulatory authorities that AAMI can be identified using criteria that are accepted in the medical community, that both the deficit in cognitive performance associated with the condition and its subsequent improvement can be measured and that the improvement is clinically meaningful, we will not obtain the regulatory approval required to market ispronicline for AAMI.

If clinical trials for our product candidates are prolonged or delayed, we would be unable to commercialize our product candidates on a timely basis, which would require us to incur additional costs and delay our receipt of any revenues from potential product sales.

We cannot predict whether we will encounter problems with any of our completed, ongoing or planned clinical trials that will cause us or any regulatory authority to delay or suspend those clinical trials or delay the analysis of data derived from them. A number of events, including any of the following, could delay the completion of our ongoing and planned clinical trials and negatively impact our ability to obtain regulatory approval for, and to market and sell, a particular product candidate:

- conditions imposed on us by the FDA or any foreign regulatory authority regarding the scope or design of our clinical trials;
- delays in recruiting and enrolling patients or volunteers into clinical trials;
- delays in obtaining, or our inability to obtain, required approvals from institutional review boards or other reviewing entities at clinical sites selected for participation in our clinical trials;
- insufficient supply or deficient quality of our product candidates or other materials necessary to conduct our clinical trials;
- lower than anticipated retention rate of subjects and patients in clinical trials;
- negative or inconclusive results from clinical trials, or results that are inconsistent with earlier results, that necessitate additional clinical study;
- serious and unexpected drug-related side effects experienced by subjects and patients in clinical trials; or
- failure of our third-party contractors to comply with regulatory requirements or otherwise meet their contractual obligations to us in a timely manner.

Clinical trials require sufficient patient enrollment, which is a function of many factors, including the size of the patient population, the nature of the trial protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial. Delays in patient enrollment can result in increased costs and longer development times. We previously experienced delays in patient enrollment for our Phase II clinical trial of ispronicline in persons with MCI. In that trial, we limited the eligible patient population to persons whose condition was sufficiently severe to qualify for a diagnosis of MCI, but not severe enough to qualify for a diagnosis of dementia. Similarly, in our planned Phase II clinical trial of ispronicline as a stand-alone treatment for mild Alzheimer's disease, we plan to limit the eligible patient population to persons diagnosed with Alzheimer's disease, but whose condition has not yet progressed from the mild stage of Alzheimer's disease to the moderate stage. As a result of these inclusion limits, we could experience delays in recruitment for that Alzheimer's disease trial similar to those that we experienced in our MCI trial. In addition, our planned design of that trial would require some of the Alzheimer's disease patients to be assigned randomly into a dosing group that would receive placebo instead of ispronicline. Those patients would not receive any medication for the duration of the trial. As a result, Alzheimer's disease patients or their caregivers may be unwilling or unable to give informed consent to participate in the trial, which would result in delays in patient enrollment. Our failure to enroll patients in a clinical trial could delay the completion of the clinical trial beyond our current expectations. In addition, the FDA could require us to conduct clinical trials with a larger number of subjects than we have projected for any of our product candidates. We may not be able to enroll a sufficient number of patients in a timely or cost-effective manner. Furthermore, enrolled patients may drop out of our clinical trials, which could impair the validity or statistical significance of the clinical trials.

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Prior to commencing clinical trials in the United States, we must submit an IND to the FDA. We conducted our Phase I clinical trial for our product candidate TC-2696 outside the United States and have not submitted an IND to enable us to conduct clinical trials of that product candidate in the United States.

We do not know whether our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, if at all. Delays in our clinical trials will result in increased development costs for our product candidates. In addition, if our clinical trials are delayed, our competitors may be able to bring products to market before we do and the commercial viability of our product candidates could be limited.

In particular, in the second half of 2005, we plan to initiate a Phase II clinical trial of ispronicline as an add-on therapy to a currently approved treatment for mild to moderate Alzheimer's disease. Although we have conducted four Phase I clinical trials of ispronicline, we have not conducted, and do not plan to conduct, a Phase I clinical trial to evaluate the safety and tolerability of ispronicline when taken together with any other drug. The FDA may require that we conduct a Phase I clinical trial to evaluate the safety and tolerability of ispronicline when taken together with the approved treatment for Alzheimer's disease before we initiate our Phase II clinical trial, which would delay and increase the cost of our clinical development of ispronicline as an add-on therapy for Alzheimer's disease.

In addition, we plan to file an IND and initiate a Phase I clinical trial of TC-1827, our product candidate for cognitive impairment associated with schizophrenia, in the first half of 2005. In one preclinical study of TC-1827 conducted with monkeys, two of ten monkeys that were given high doses of TC-1827 were found at the end of the study to have low levels of platelets in their blood, a condition known as thrombocytopenia. We plan to repeat the study in which thrombocytopenia was observed at the same time as we conduct our initial Phase I clinical trial of TC-1827. It is possible that the FDA will require that we complete the study in monkeys before commencing the Phase I trial. If the FDA were to require that we conduct the study in monkeys before we conduct Phase I clinical development of TC-1827, our development of TC-1827 for cognitive impairment associated with schizophrenia would be delayed.

Our product candidates will remain subject to ongoing regulatory review even if they receive marketing approval. If we fail to comply with continuing regulations, we could lose these approvals and the sale of our products could be suspended.

Even if we receive regulatory approval to market a particular product candidate, the approval could be conditioned on us conducting additional costly post-approval studies or could limit the indicated uses included in our labeling. Moreover, the product may later cause adverse effects that limit or prevent its widespread use, force us to withdraw it from the market or impede or delay our ability to obtain regulatory approvals in additional countries. In addition, the manufacturer of the product and its facilities will continue to be subject to FDA review and periodic inspections to ensure adherence to applicable regulations. After receiving marketing approval, the manufacturing, labeling, packaging, adverse event reporting, storage, advertising, promotion and record keeping related to the product will remain subject to extensive regulatory requirements. We may be slow to adapt, or we may never adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements.

If we fail to comply with the regulatory requirements of the FDA and other applicable U.S. and foreign regulatory authorities or previously unknown problems with our products, manufacturers or manufacturing processes are discovered, we could be subject to administrative or judicially imposed sanctions, including:

- restrictions on the products, manufacturers or manufacturing processes;
- warning letters;
- civil or criminal penalties;
- fines;
- injunctions;
- product seizures or detentions;

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- import bans;
- voluntary or mandatory product recalls and publicity requirements;
- suspension or withdrawal of regulatory approvals;
- total or partial suspension of production; and
- refusal to approve pending applications for marketing approval of new drugs or supplements to approved applications.

Because we have a number of compounds and are considering a variety of target indications, we may expend our limited resources to pursue a particular candidate or indication and fail to capitalize on candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we must focus on research programs and product candidates for the specific indications that we believe are the most promising. As a result, we may forego or delay pursuit of opportunities with other product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Through 2004, we spent managerial and financial resources on clinical trials for two product candidates that we have ceased developing. We may in the future spend our resources on other research programs and product candidates for specific indications that ultimately do not yield any commercially viable products. Furthermore, if we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights.

We may not be successful in our efforts to identify or discover additional product candidates.

A key element of our strategy is to develop and commercialize drugs that selectively target specific NNR subtypes. We seek to do so through our understanding of the role of specific NNRs in the nervous system, our scientific expertise and the use of Pentad.

Other than ispronicline, TC-2696 and Inversine, all of our product candidates are at a preclinical stage. A significant portion of the research that we are conducting involves new and unproven compounds. Research programs to identify new product candidates require substantial technical, financial and human resources. These research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential product candidates; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be effective products.

In particular, in one preclinical study of TC-1827 conducted with monkeys, two of ten monkeys that were given high doses of TC-1827 were found at the end of the study to have low levels of platelets in their blood, a condition known as thrombocytopenia. We plan to repeat the study in which thrombocytopenia was observed in the first half of 2005. If thrombocytopenia is observed when the study is repeated, we may have to discontinue further development of TC-1827.

If we are unable to develop suitable product candidates through internal research programs, we will not be able to increase our revenues in future periods, which could result in significant harm to our financial position and adversely impact our stock price. Any additional product candidates that we are able to develop through our internal research programs will require the commitment of substantial time and financial resources for further preclinical research and clinical development.

Risks Related to Our Dependence on Third Parties

We will depend on collaborations with third parties for the development and commercialization of some of our product candidates. If these collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We intend to selectively enter into collaboration agreements with leading pharmaceutical and biotechnology companies where our potential collaborator has particular therapeutic expertise in a target indication or where the target indication represents a large, primary care market. We will have limited control over the amount and timing of resources that our potential collaborators dedicate to the development of our licensed product candidates. Our ability to generate revenues from our collaborators will depend on our collaborators' abilities to establish the safety and efficacy of our product candidates, to obtain regulatory approvals and to achieve market acceptance.

In general, strategic collaborations involving our product candidates pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue further development and commercialization of our product candidates or may elect not to continue or renew research and development programs based on preclinical or clinical trial results, changes in their strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive;
- a collaborator with marketing and distribution rights to one or more products may not commit enough resources to their marketing and distribution;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- disputes may arise between us and the collaborators that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development of the applicable product candidates.

Collaboration agreements may not lead to development of product candidates in the most efficient manner or at all. For example, a collaborative research and development agreement that we entered into with Aventis Pharma for the development of our compounds for the treatment or prevention of Alzheimer's disease terminated on January 2, 2005. None of our compounds that were subject to this agreement were advanced into clinical development under the agreement. As a result of the termination, we may pursue the development and commercialization of our product candidates, including ispronicline, for Alzheimer's disease, but without funding from Aventis.

In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on

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our product development program could be delayed, diminished or terminated. For example, in 2004, Sanofi-Synthelabo acquired a controlling interest in Aventis. We believe that Sanofi-Synthelabo has its own program to develop compounds that act on neuronal nicotinic acetylcholine receptors to treat Alzheimer's disease. This may reduce the likelihood that Aventis will pursue the development and commercialization of compounds that would entitle us to payments under another collaboration agreement that we entered into with Aventis relating to the development of Aventis compounds for the treatment of Alzheimer's disease and other diseases of the central nervous system. The research term of this agreement expired in December 2004, and Aventis has informed us that it does not intend to extend the research term. We are only eligible to receive future payments from Aventis for any compounds that are selected for further development within six months after the expiration of the research term.

If we do not establish additional collaborations, we may have to alter our development plans.

Our drug development programs and potential commercialization of our product candidates will require substantial additional cash to fund expenses. Our strategy includes selectively collaborating with leading pharmaceutical and biotechnology companies to assist us in furthering development and potential commercialization of some of our product candidates. We intend to do so especially for target indications in which our potential collaborator has particular therapeutic expertise or that involve a large, primary care market that must be served by large sales and marketing organizations. We face significant competition in seeking appropriate collaborators and these collaborations are complex and time-consuming to negotiate and document. We may not be able to negotiate collaborations on acceptable terms, or at all. If that were to occur, we may have to curtail the development of a particular product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of our sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we will not be able to bring our product candidates to market and generate product revenue.

If our contract manufacturers fail to devote sufficient resources to our concerns, or if their performance is substandard, our clinical trials and product introductions may be delayed or there may be a shortage of commercial supply.

Our product candidates require precise, high quality manufacturing. We have limited internal manufacturing capability. We have historically manufactured our product candidates only in small quantities for preclinical testing and have contracted with third parties to manufacture, in collaboration with us, our product candidates for clinical trials and, in the case of Inversine, for commercial sale. If any of our product candidates is approved by the FDA or by foreign regulatory authorities for marketing and sale, it will need to be manufactured in substantially larger, commercial quantities. Our experience in the manufacture of drugs in commercial quantities is limited to our contractual arrangements with third parties to manufacture Inversine and its active ingredient.

We currently rely on various third-party contract manufacturers, including Siegfried Ltd., for our product candidates and we intend to continue to rely on third-party manufacturers to supply, store and distribute our product candidates for our clinical trials and to manufacture commercial supplies of any product candidate that is approved for sale. Our reliance on third-party manufacturers will expose us to risks that could delay or prevent the initiation or completion of our clinical trials, the submission of applications for regulatory approvals, the approval of our products by the FDA or the commercialization of our products or result in higher costs or lost product revenues. In particular, contract manufacturers:

- could encounter difficulties in achieving volume production, quality control and quality assurance and suffer shortages of qualified personnel, which could result in their inability to manufacture sufficient quantities of drugs to meet our clinical schedules or to commercialize our product candidates;
- could terminate or choose not to renew the manufacturing agreement, based on their own business priorities, at a time that is costly or inconvenient for us;

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- could fail to establish and follow FDA-mandated current good manufacturing practices, or cGMPs, required for FDA approval of our product candidates or fail to document their adherence to cGMPs, either of which could lead to significant delays in the availability of material for clinical study and delay or prevent filing or approval of marketing applications for our product candidates; and
- could breach, or fail to perform as agreed under, the manufacturing agreement.

We expect to rely initially on a single contract manufacturer for each of our product candidates. Currently, we have separate arrangements with third-party manufacturers, each of which is a sole supplier to us, for the active ingredient of Inversine and the finished tablets of Inversine. Changing these or any manufacturer that we subsequently engage for a particular product or product candidate may be difficult, as the number of potential manufacturers is limited and we will have to compete with third parties for access to those manufacturing facilities. cGMP manufacturing processes and procedures typically must be reviewed and approved by the FDA and changing manufacturers may require re-validation of any new facility for cGMP compliance, which would likely be costly and time-consuming. We may not be able to engage replacement manufacturers on acceptable terms quickly or at all. In addition, our contract manufacturers located in foreign countries may be subject to import limitations or bans. As a result, if any of our contract manufacturers is unable, for whatever reason, to supply the contracted amounts of Inversine or any other product that we successfully bring to market, a shortage would result which would have a negative impact on our revenues.

Drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the United States Drug Enforcement Agency and corresponding state and foreign agencies to ensure strict compliance with cGMPs, other government regulations and corresponding foreign standards. While we are obligated to audit the performance of third-party contractors, we do not have control over our third-party manufacturers' compliance with these regulations and standards. Failure by our third-party manufacturers or us to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of the government to grant pre-market approval of drugs, delays, suspension or withdrawal of approvals, seizures or recalls of product, operating restrictions and criminal prosecutions.

If third parties on which we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our product candidates. We depend on independent clinical investigators and, in some cases, contract research organizations and other third-party service providers to conduct the clinical trials of our product candidates and expect to continue to do so. We rely heavily on these parties for successful execution of our clinical trials, but we do not control many aspects of their activities. Nonetheless, we are responsible for confirming that each of our clinical trials is conducted in accordance with its general investigational plan and protocol. Moreover, the FDA requires us to comply with regulations and standards, commonly referred to as good clinical practices, for conducting and recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the trial participants are adequately protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory requirements or the respective trial plans and protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates or result in enforcement action against us.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property effectively, our competitors may develop and market similar products and the value of our technology and our ability to compete would be damaged.

Our continued success depends significantly on our ability to obtain and maintain meaningful intellectual property protection for our product candidates, technology and know-how. We generally seek to protect our

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compounds and technologies by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology that is important to the development of our business. We file patent applications directed to our product candidates in an effort to establish intellectual property positions regarding new chemical entities and uses in the treatment of disease.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. Our ability to maintain and solidify our proprietary position for our technology will depend on our success in obtaining effective patent claims and enforcing claims that are granted. We do not know whether any of our patent applications or those patent applications that we license will result in the issuance of any patents. For example, we have a pending patent application covering the composition of TC-2216, our product candidate for depression and anxiety disorders, but currently have no issued patent that covers that product candidate. Moreover, our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated, rendered unenforceable or circumvented, any of which could limit our ability to stop competitors from marketing related products. In addition, the rights granted under any issued patents may not provide us with competitive advantages against competitors with similar compounds or technologies. Furthermore, our competitors may independently develop similar technologies in a manner that does not infringe our patents or other intellectual property.

Although we own or otherwise have rights to a number of patents, these patents may not effectively exclude competitors from engaging in activities that compete with us. Furthermore, the issuance of a patent is not conclusive as to its validity or enforceability, and third parties may challenge the validity or enforceability of our patents. Because patent applications in the United States and many foreign countries are confidential for a period of time after filing, and because publications of discoveries in the scientific literature often lag behind actual discoveries, we cannot be certain that we were the first to make the inventions claimed in our issued U.S. patents or pending patent applications, or that we were the first to file for protection of the inventions set forth in the foreign patents or patent applications. It is possible that a competitor may successfully challenge our patents or that challenges will result in the elimination or narrowing of patent claims and, therefore, reduce our patent protection.

Because of the extensive time required for development, testing and regulatory review of a new drug, it is possible that any related patent may expire before any of our product candidates can be commercialized or remain in force for only a short period following commercialization. In either case, this would reduce any advantages of the patent. The patent laws of various foreign countries in which we intend to compete may not protect our intellectual property to the same extent as the laws of the United States. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection.

If we are unable to protect the confidentiality of our proprietary information and know-how, the commercial value of our technology and product candidates could be reduced.

In addition to patents, we rely on protection of trade secrets, know-how and confidential and proprietary information to maintain our competitive position. To maintain the confidentiality of trade secrets and proprietary information, we generally enter into confidentiality agreements with our employees, consultants, contractors and collaborative partners upon the commencement of our relationship with them. These agreements typically require that all confidential information developed by the individual or made known to the individual by us during the course of the individual's relationship with us be kept confidential and not disclosed to third parties. However, we may not obtain these agreements in all circumstances, and individuals with whom we have these agreements may not comply with their terms. Even if obtained, these agreements may not provide meaningful protection for our trade secrets or other proprietary information or an adequate remedy in the event of their unauthorized use or disclosure. The loss or exposure of our trade secrets or other proprietary information could impair our competitive position.

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We also typically enter into agreements with employees that provide inventions conceived by them in the course of rendering services to us are our exclusive property and, where appropriate, we enter into similar agreements with consultants and contractors. To the extent that our employees, consultants or contractors use technology or know-how owned by others in their work for us, disputes may arise as to the rights in related inventions.

If we fail to comply with our obligations in our intellectual property licenses with third parties, we could lose license rights that are important to our business.

We are a party to various license agreements. In particular, we license patent rights for a method of use of TC-2696, our product candidate for pain, and TC-5214, one of our product candidates for depression. We may enter into additional licenses in the future. Our existing licenses impose, and we expect future licenses will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license, in which event we might not be able to market any product that is covered by the licensed patents.

Our patent protection for any particular compound may be limited to a particular method of use or indication such that, if a third party were to obtain approval of the compound for use in another indication, we could be subject to competition arising from off-label use.

Although we generally seek the broadest patent protection available for our proprietary compounds, we may not be able to obtain patent protection for the actual composition of any particular compound and may be limited to protecting a new method of use for the compound or otherwise restricted in our ability to prevent others from exploiting the compound. For example, we currently rely on method of use patent coverage in the United States for TC-5214, one of our product candidates for depression. If we are unable to obtain patent protection for the actual composition of any compound that we seek to develop and commercialize and must rely on method of use patent coverage, we would likely be unable to prevent others from manufacturing or marketing that compound for any use that is not protected by our patent rights. If a third party were to receive marketing approval for the compound for another use, physicians could nevertheless prescribe it for indications that are not described in the product's labeling or approved by the FDA or other regulatory authorities. Even if we have patent protection for the prescribed indication, as a practical matter, we would have little recourse as a result of this off-label use. In that event, our revenues from the commercialization of the compound would likely be adversely affected.

We may be involved in lawsuits to protect or enforce our patents that could be expensive and time-consuming.

We may initiate patent litigation against third parties to protect or enforce our patent rights and we may be similarly sued by third parties. We may also become subject to interference or opposition proceedings conducted in the patent and trademark offices of various countries to determine our entitlement to patents. The defense and prosecution of intellectual property suits, interference proceedings and related legal and administrative proceedings, if necessary, would be costly and divert our technical and management personnel from conducting our business. Moreover, we may not prevail in any of these suits. An adverse determination of any litigation or proceeding could put our patents at risk of being invalidated or narrowly interpreted and our patent applications at risk of not being issued and could prevent us from protecting our rights, particularly in countries where the laws may not protect such rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that disclosure of some of our confidential information could be compelled and the information compromised. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments that, if perceived as negative by securities analysts or investors, could have a substantial adverse effect on the trading price of our common stock.

Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our development and commercialization efforts.

Our success depends in part on avoiding the infringement of other parties' patents and proprietary rights. Patents may issue from patent applications of which we are unaware, and avoiding patent infringement may be difficult. We may infringe or it may be alleged that we infringe third-party patents. If a third party were to file a patent infringement suit against us, we could be forced to stop or delay research, development, manufacturing or sales of any infringing product in the country or countries covered by the patent infringed, unless we can obtain a license from the patent holder. Any necessary license may not be available on acceptable terms or at all, particularly if the third party is developing or marketing a product competitive with the infringing product. Even if we are able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property.

We also may be required to pay substantial damages to the patent holder in the event of an infringement. These damages could in some circumstances be triple the actual damages the patent holder incurs. If we have supplied infringing products to third parties for marketing or have licensed third parties to manufacture, use or market infringing products, we may be obligated to indemnify these third parties for any damages they may be required to pay to the patent holder and for any losses they may sustain themselves as a result.

Any successful infringement action brought against us may also adversely affect marketing of the infringing product in other markets not covered by the infringement action, as well as our marketing of other products based on similar technology. Furthermore, we may suffer adverse consequences from a successful infringement action against us even if the action is subsequently reversed on appeal, nullified through another action or resolved by settlement with the patent holder. The damages or other remedies awarded, if any, may be significant. As a result, any infringement action against us would likely delay the regulatory approval process, harm our competitive position, be very costly and require significant time and attention of our key management and technical personnel.

Risks Related to Commercialization

Even if approved for marketing, our product candidates may not gain market acceptance and may fail to generate significant revenues.

The commercial success of any of our product candidates for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by the medical community and third-party payors as clinically useful, cost-effective and safe. Many of the product candidates that we are developing are based upon technologies or methods of treatment that are relatively new and unproven. As a result, it may be more difficult for us to achieve market acceptance of our products.

The degree of market acceptance of any drug depends on a number of factors, such as:

- its demonstration of efficacy and safety in clinical trials;
- its superior efficacy as compared to alternative treatment methods and its side effect profile;
- its cost-effectiveness and the availability of insurance or other third-party reimbursement;
- its convenience and ease of administration;
- the timing of its market entry relative to competitive treatments;
- the extent and success of marketing and sales efforts; and
- the product labeling or product insert required by the FDA or regulatory authorities in other countries.

In addition, perceptions about the relationship or similarity between our product candidates and nicotine could limit their market potential. Our product candidates derive their medical effects by interacting with NNRs.

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Nicotine, which can have significantly negative health effects, also interacts with NNRs. Accordingly, our product candidates may be perceived by some to be nicotine or to be closely related to nicotine, particularly in light of the shared derivative names, “nicotine” and neuronal “nicotinic” acetylcholine receptors, and the fact that our company was launched originally as a research group within, and then as a subsidiary of, R.J. Reynolds Tobacco Company. This potential perception could result in a reluctance by patients to take, or by physicians to prescribe, any of our product candidates that receives marketing approval, which would affect our revenues.

We currently have limited sales, marketing and distribution experience and no internal sales or distribution capabilities. If we are unable to enter into collaborations or other arrangements with third parties to market and sell our product candidates or to develop our own internal marketing capability, we may not be successful in commercializing our products.

We currently have limited sales, marketing and distribution experience. Our experience is limited to a contractual arrangement with a third party to distribute Inversine, which we acquired in 2002 and which generates only limited sales. We currently have no internal sales or distribution capabilities. Although we intend to build an internal sales force and expand our marketing capabilities in areas where specialists heavily influence our target markets, such as neurology and psychiatry, we also intend to seek to further augment our sales, marketing and distribution capabilities through arrangements with third parties. In particular, our strategy includes selectively entering into collaborations and other strategic alliances with respect to product candidates for disease indications with sales and distribution characteristics requiring a large sales force. There are risks involved with establishing our own sales force and marketing and distribution capabilities, as well as in entering into arrangements with third parties to perform these services. Developing our own sales force will be expensive and time-consuming and could delay any product launch. We may not be successful in entering into arrangements with third parties on terms that are favorable to us or at all. Also, we would have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell, market or distribute our products effectively. If we do not establish sales and distribution capabilities successfully, either on our own or in collaboration with third parties, we may not successfully commercialize our products.

Unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives applicable to our product candidates could limit our potential product revenue.

The regulations governing drug pricing and reimbursement vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed and, in many of these countries, the pricing review period begins only after approval is granted. In some countries, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we monitor these regulations, our product candidates are currently in the development stage and we will not be able to assess the impact of price regulations for at least several years. As a result, we may obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay the commercial launch of the product and may negatively impact the revenues we are able to derive from sales in that country.

Successful commercialization of our products will also depend in part on the extent to which coverage and adequate payment for our products will be available from government health administration authorities, private health insurers and other third-party payors. If we succeed in bringing a product candidate to the market, it may not be considered cost-effective and reimbursement to the patient may not be available or sufficient to allow us to sell it at a satisfactory price. Because our product candidates are in the development stage, we are unable at this time to determine their cost-effectiveness. We may need to conduct expensive studies in order to demonstrate cost-effectiveness. Moreover, third-party payors frequently require that drug companies provide them with predetermined discounts from list prices and are increasingly challenging the prices charged for medical products. Because our product candidates are in the development stage, we do not know the level of reimbursement, if any, we will receive for any products that we are able to successfully develop. If the reimbursement for any of our product candidates is inadequate in light of our development and other costs, our ability to achieve profitability could be affected.

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We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory proposals to change the healthcare system in the United States and other major healthcare markets have been proposed and adopted in recent years. For example, the U.S. Congress has enacted a limited prescription drug benefit for Medicare recipients as part of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. While the program established by this statute may increase demand for any products that we are able to successfully develop, if we participate in this program, our prices will be negotiated with drug procurement organizations for Medicare beneficiaries and are likely to be lower than prices we might otherwise obtain. If successfully developed, ispronicline, our product candidate for conditions marked by cognitive impairment that afflict the elderly, could be particularly affected by this law because of the product candidate's elderly target patient population. Non-Medicare third-party drug procurement organizations may also base the price they are willing to pay on the rate paid by drug procurement organizations for Medicare beneficiaries. In addition, ongoing initiatives in the United States have and will continue to increase pressure on drug pricing. The announcement or adoption of any such initiative could have an adverse effect on potential revenues from any product candidate that we may successfully develop.

If our competitors develop and market drugs that are less expensive, more effective or safer than ours, if they develop and market products faster than we do, or if they have better sales and marketing capabilities than we do, any products we are able to commercialize may not generate initial or ongoing revenues.

The development and commercialization of new drugs is highly competitive. Our business is characterized by extensive research efforts and rapid developments. We expect intense competition in our target markets as new products and advanced technologies become available. Our competitors include large pharmaceutical, biotechnology and other companies and research institutions, many of which have greater financial, technical and other resources and personnel and more experience in research, clinical development, regulatory and drug commercialization than we have. Our competitors may:

- develop products that are more effective, safer, more convenient or less costly than our product candidates;
- obtain FDA or other regulatory approval for their products more rapidly than we do;
- adapt more quickly to new technologies and scientific advances;
- initiate or withstand substantial price competition more successfully than we can;
- have greater success in recruiting skilled scientific workers from the limited pool of available talent;
- obtain more effective intellectual property protection than we have;
- negotiate third-party licensing and collaboration arrangements more effectively than we do; and
- take advantage of acquisition or other opportunities more readily than we do.

Competitive products may render our product candidates obsolete or noncompetitive before we can recover our development or commercialization expenses.

We also face substantial competition from therapies designed to target NNRs. We believe that several prominent pharmaceutical companies have product candidates that target NNRs in development, including Pfizer, with a compound in Phase III clinical trials for smoking cessation, and Abbott Laboratories, with one compound in Phase I clinical trials for pain and another in Phase II clinical trials for Alzheimer's disease, ADHD and schizophrenia. We expect that we will face increased competition in the future if therapies that target NNRs are further validated and companies initiate or expand programs focused on NNRs, whether independently or by collaboration or acquisition.

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Any products that we are able to successfully develop and commercialize in the future could be subject to competition from lower priced generic drugs. The manufacturer of a generic product could challenge our patents as invalid or not infringed and subject us to expensive litigation. We do not know if we would prevail in litigation and succeed in keeping the generic product out of the market until our patent protection expires.

If we successfully develop and obtain approval for our product candidates, we will face competition based on the safety and effectiveness of our products, the timing and scope of regulatory approvals, the availability and cost of supply, marketing and sales capabilities, reimbursement coverage, price, patent position and other factors. Our competitors may develop or commercialize more effective or more affordable products, or obtain more effective patent protection, than we do. Accordingly, our competitors may commercialize products more rapidly or effectively than we do.

If approved, our product candidates will compete for a share of the existing market with numerous approved products. There is currently no approved product either for AAMI or for cognitive impairment associated with schizophrenia. We believe that the primary competitive products for use in the other indications that we are currently targeting include:

- for mild to moderate Alzheimer's disease, acetylcholinesterase inhibitors such as Aricept from Pfizer, Reminyl from Johnson & Johnson and Exelon from Novartis and for moderate to severe Alzheimer's disease, Namenda from Forest Laboratories, which acts by regulating the neurotransmitter glutamate;
- for pain, non-steroidal anti-inflammatory drugs such as Celebrex from Pfizer and opioids such as OxyContin from Purdue Pharma;
- for depression, selective serotonin reuptake inhibitors such as Prozac from Eli Lilly, Paxil from GlaxoSmithKline, Zoloft from Pfizer, Celexa and Lexapro from Forest Laboratories and the dual uptake inhibitor Effexor from Wyeth;
- for schizophrenia, anti-psychotics such as Zyprexa from Eli Lilly, Risperdal from Johnson & Johnson and Abilify from Bristol-Myers Squibb; and
- for smoking cessation, Zyban from GlaxoSmithKline.

We may have substantial exposure to product liability claims and may not have adequate insurance to pay them.

We face an inherent business risk of exposure to product liability claims if the use of our products is alleged to have resulted in harm to others. This risk exists for product candidates in clinical trials, whether or not the product candidate is subsequently approved for commercial sale, as well as for products in commercial distribution. Any product liability claim arising in the future against us or any third party that we have agreed to indemnify, regardless of its merit or eventual adjudication, could be costly and significantly divert management's attention from conducting our business or adversely affect our reputation and the demand for our products.

We have secured product liability insurance coverage with limits of \$8 million per occurrence and \$8 million in the aggregate. Our current insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may incur. We intend to expand our coverage with respect to any products for which we obtain marketing approval. However, additional insurance may not be available to cover our potential liabilities fully or may be prohibitively expensive. In addition, some potential product liability claims may be excluded from coverage under the terms of the policy. Our inability to obtain adequate insurance coverage at an acceptable cost could prevent or impede the commercialization of our product candidates.

Our business activities involve hazardous materials, which could subject us to significant liability.

Our research and development activities involve, and any future manufacturing processes that we conduct may involve, the use of hazardous materials, including hazardous chemicals and radioactive materials.

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Accordingly, we are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these materials. We incur significant costs to comply with these laws and regulations. Moreover, despite precautionary procedures that we implement, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident or environmental discharge, we may be held liable for any resulting damages. We do not carry insurance against the risk of contamination or injury from hazardous materials.

If our promotional activities fail to comply with the regulations and guidelines of the FDA and other applicable regulatory authorities, we may be subject to warnings or enforcement actions that could harm our business.

Physicians may prescribe drugs for uses that are not described in the product's labeling or for uses that differ from those tested in clinical studies and approved by the FDA or similar regulatory authorities in other countries. Regulatory authorities generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications on the subject of off-label use. Companies cannot actively promote approved drugs for off-label uses but, in some countries outside of the European Union, they may disseminate articles published in peer-reviewed journals that discuss off-label uses of approved products to physicians. To the extent allowed, we may in the future disseminate peer-reviewed articles on our products to physicians. We do not currently promote Inversine for off-label use in the treatment of any neuropsychiatric disorder. However, if we undertake any promotional activities in the future for Inversine or any other product candidate that we are able to commercialize and our activities fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities.

Risks Related to Employees and Managing Growth

If we lose our key personnel or are unable to attract and retain additional skilled personnel, we may be unable to successfully develop and commercialize our product candidates or effectively compete in our industry.

Our performance depends substantially on the performance of our senior management and key scientific, technical and managerial personnel, including our Chief Executive Officer and President, J. Donald deBethizy, and our Vice President, Clinical Development and Regulatory Affairs, Geoffrey C. Dunbar. Our executive officers, including these individuals, can terminate their employment agreements with us at any time. The loss of the services of any of our executive officers may significantly delay or prevent the achievement of product research and development and other business objectives. We maintain key man life insurance policies on Dr. deBethizy and Dr. Dunbar, among other executive officers. We also rely on consultants and advisors to assist us in formulating our research and development strategy. All of our consultants and advisors are either self-employed or employed by other organizations, and they may have other commitments, including consulting or advisory contracts with other organizations, that may affect their ability to contribute to us.

Our ability to operate successfully and manage our potential future growth will depend on our ability to identify, recruit and retain additional qualified scientific, technical, financial and managerial personnel. There is currently a shortage of skilled executives in our industry, and we face intense competition for such personnel. We may not be able to continue to attract and retain personnel with the advanced qualifications necessary for the growth of our business.

We may encounter difficulties in managing our growth, which could increase our losses.

We expect the number of our employees and the scope of our operations to grow following completion of this offering. Continued growth may place a significant strain on our managerial, operational and financial resources, in particular as we expand our focus beyond drug discovery and development to commercialization. To manage our anticipated growth, we must continue to implement and improve our managerial, operational and financial systems and controls and reporting processes and procedures, to expand our facilities and to continue to recruit and train additional qualified personnel. We may not be able to manage our growth effectively. Moreover, we may discover deficiencies in existing systems and controls that could expose us to an increased risk of incurring financial or accounting irregularities or fraud.

Risks Related to Our Common Stock and this Offering

The market price of our common stock may be highly volatile. You may not be able to resell your shares at or above the initial public offering price.

There has been no public market for our common stock prior to this offering, and it is possible that no active trading market for our common stock will develop or continue following this offering. You may not be able to sell your shares quickly or at the market price if trading in our common stock is not active. The initial public offering price for the shares will be determined by negotiation with representatives of the underwriters and may not be indicative of prices that will prevail in the trading market. Please see “Underwriters” for more information regarding our arrangements with the underwriters and the factors to be considered in setting the initial public offering price.

We expect that the trading price of our common stock is likely to be highly volatile in response to factors that are beyond our control. The stock market in general has previously experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile and have experienced fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause a decline in the value of your shares.

If you purchase shares of our common stock in this offering, you will experience immediate and substantial dilution of your investment.

The offering price of our common stock will be substantially higher than the net tangible book value of \$(61.97) per share of our existing capital stock as of September 30, 2004. As a result, based on an assumed initial public offering price of _____, purchasers of our common stock in this offering will incur immediate and substantial dilution of \$ _____ per share, representing the difference between our pro forma net tangible book value per share after giving effect to this offering and the assumed initial public offering price, and will incur additional dilution if outstanding stock options and warrants with exercise prices below the public offering price are exercised. See “Dilution” for a more detailed discussion of the dilution new investors will incur in this offering.

If our operating results fluctuate significantly, our stock price may decline and result in losses to you.

Our operating results are likely to fluctuate significantly from quarter to quarter and year to year. These fluctuations could cause our stock price to decline. Some of the factors that could cause our operating results to fluctuate include:

- our or our collaborators’ inability to successfully complete preclinical studies and clinical trials in a timely manner or at all, resulting in a delay in receiving, or a failure to receive, the required regulatory approvals to commercialize our product candidates;
- the timing of regulatory approvals or other regulatory actions;
- general and industry-specific economic conditions that may affect our and our collaborative partners’ research and development expenditures;
- the timing of receipts of milestone payments from our collaborative partners; and
- the expiration or termination of agreements with collaborative partners or the execution of new agreements.

Due to fluctuations in our operating results, a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors and our stock price could decline.

If our existing stockholders sell a substantial number of shares of our common stock in the public market, our stock price may decline.

Sales of a substantial number of shares of our common stock in the public market following this offering could cause the market price to decline. Such sales also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate. After this offering, we will have _____ shares of common stock outstanding based on the number of shares outstanding as of _____, 2004. If there are more shares of our common stock offered for sale than buyers are willing to purchase, the market price of our common stock may decline to a market price at which buyers are willing to purchase the offered shares and sellers remain willing to sell the shares. The number of shares of our common stock available for sale in the public market is limited by restrictions under federal securities laws and under lock-up agreements that substantially all of our stockholders have entered into with the underwriters. Except in limited circumstances, these lock-up agreements restrict our stockholders from selling or otherwise disposing of their shares for a period of 180 days after the date of this prospectus, subject to a possible extension, without the prior written consent of Deutsche Bank Securities Inc. on behalf of the underwriters. However, Deutsche Bank Securities may, in its sole discretion, release all or any portion of the common stock from the restrictions of the lock-up agreements. Deutsche Bank Securities does not have any pre-established conditions to waiving the terms of the lock-up agreements. Any determination to release any shares subject to the lock-up agreements would be based on a number of factors at the time of determination, including but not necessarily limited to the market price of the common stock, the liquidity of the trading market for the common stock, general market conditions, the number of shares proposed to be sold and the timing, purpose and terms of the proposed sale.

Additionally, of the _____ shares of our common stock that may be issued upon the exercise of options outstanding as of _____, 2004, approximately _____ shares will be vested and eligible for sale 180 days after the date of this prospectus. For a further description of the eligibility of shares for sale into the public market following the offering, see “Shares Eligible for Future Sale.” In the future, we may issue additional shares to our employees, directors or consultants, in connection with corporate alliances or acquisitions or to raise capital. Accordingly, sales of a substantial number of shares of our common stock in the public market could occur at any time.

Management may invest or spend the proceeds of this offering in ways in which you may not agree or in ways that may not yield a favorable return to our stockholders.

Management will retain broad discretion over the use of the net proceeds from this offering. Stockholders may not agree with such uses, and our use of the proceeds may not yield a significant return or any return at all for our stockholders. We intend to use the proceeds from this offering for research and development and other general corporate purposes. Because of the number and variability of factors that will determine our use of the proceeds from this offering, their ultimate use may vary substantially from their currently intended use.

Concentration of ownership among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Following the completion of this offering, our executive officers, directors and their affiliates will beneficially own or control approximately _____ % of the outstanding shares of our common stock. Accordingly, our current executive officers, directors and their affiliates will have substantial control over the outcome of corporate actions requiring stockholder approval, including the election of directors, any merger, consolidation or sale of all or substantially all of our assets or any other significant corporate transactions, as well as our management and affairs. The concentration of ownership may also delay or prevent a change of control of us at a premium price if these stockholders oppose it, even if it would benefit our other stockholders.

Provisions of our charter, bylaws and Delaware law may make an acquisition of us or a change in our management more difficult.

Certain provisions of our certificate of incorporation and bylaws that will be in effect upon the completion of this offering could discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. Stockholders who wish to participate in these transactions may not have the opportunity to do so. Furthermore, these provisions could prevent or frustrate attempts by our stockholders to replace or remove our management. These provisions:

- allow the authorized number of directors to be changed only by resolution of our board of directors;
- establish a classified board of directors, providing that not all members of the board be elected at one time;
- authorize our board of directors to issue without stockholder approval blank check preferred stock that, if issued, could operate as a “poison pill” to dilute the stock ownership of a potential hostile acquirer to prevent an acquisition that is not approved by our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit stockholder action by written consent;
- establish advance notice requirements for stockholder nominations to our board of directors or for stockholder proposals that can be acted on at stockholder meetings;
- limit who may call stockholder meetings; and
- require the approval of the holders of 66 ²/₃% of the outstanding shares of our capital stock entitled to vote in order to amend certain provisions of our certificate of incorporation and bylaws.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may, unless certain criteria are met, prohibit large stockholders, in particular those owning 15% or more of our outstanding voting stock, from merging or combining with us for a prescribed period of time.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the statements under “Prospectus Summary,” “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” “Business” and elsewhere in this prospectus constitute forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. While we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus, we caution you that these statements are based on a combination of facts and factors currently known by us and projections of the future, about which we cannot be certain. Many important factors affect our ability to achieve our objectives, including the following:

- the size and growth potential of the potential markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates;
- our plans to research, develop and commercialize our product candidates;
- the success of our clinical trials;
- our ability to obtain and maintain regulatory approval for our product candidates;
- our use of the proceeds from this offering;
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing, and our ability to obtain additional financing;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- the successful development of our marketing capabilities;
- the success of competing therapies that are or become available; and
- the performance of third-party manufacturers with which we contract to provide a supply of our product candidates.

In addition, you should refer to the “Risk Factors” section of this prospectus for a discussion of other important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. The Private Securities Litigation Reform Act of 1995 and Section 27A of the Securities Act of 1933 do not protect any forward-looking statements that we make in connection with this offering.

You should read this prospectus completely. In some cases, you can identify forward-looking statements by the following words: “may,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “anticipate,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “ongoing” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. We may not update these forward-looking statements even though our situation may change in the future. We qualify all the forward-looking statements contained in this prospectus by the foregoing cautionary statements.

USE OF PROCEEDS

We estimate that our net proceeds from the sale of _____ shares of our common stock in this offering will be approximately \$ _____ million, or approximately \$ _____ million if the underwriters exercise their over-allotment option in full, assuming an initial public offering price of \$ _____ per share and after deducting estimated underwriting discounts and commissions and offering expenses payable by us.

We estimate that we will use:

- approximately \$ _____ million of these net proceeds to fund further development of ispronidine, our product candidate for conditions marked by cognitive impairment that afflict the elderly, including Alzheimer's disease and AAMI;
- approximately \$ _____ million of these net proceeds to fund further development of TC-1827, our product candidate for cognitive impairment associated with schizophrenia;
- approximately \$ _____ million of these net proceeds to fund further development of TC-2696, our product candidate for acute post-operative pain;
- approximately \$ _____ million of these net proceeds to complete our ongoing Phase II clinical trial of Inversine as an add-on therapy in patients with major depressive disorder;
- approximately \$ _____ million of these net proceeds to conduct the additional preclinical toxicology studies necessary to support an IND for clinical trials of TC-2216; and
- approximately \$ _____ million of these net proceeds to fund general and administrative expenses, working capital needs and other general corporate purposes.

We may also use a portion of the proceeds for the potential acquisition of, or investment in, technologies, products or companies that complement our business, although we have no current understandings, commitments or agreements to do so.

The amounts and timing of our actual expenditures may vary significantly depending upon numerous factors, including the progress and status of our development and commercialization efforts, the amount of proceeds actually raised in this offering, the amount of cash generated through our existing strategic collaborations, any additional strategic collaborations into which we may enter and sales of Inversine, and our operating costs and capital expenditures. Accordingly, our management will have significant flexibility in applying the net proceeds of this offering. We may change the allocation of use of these proceeds as a result of contingencies such as the progress and results of our clinical trials and other research and development activities, the establishment of collaborations, the results of our commercialization efforts, our manufacturing requirements and regulatory or competitive developments.

We do not expect our existing capital resources and the net proceeds from this offering to be sufficient to enable us to fund the completion of the development of any of our product candidates. We expect that the net proceeds from this offering, together with our existing capital resources, will be sufficient to enable us to initiate our planned Phase II clinical trial of ispronidine as an add-on therapy for mild to moderate Alzheimer's disease and to complete our planned Phase II clinical trial of ispronidine as a stand-alone treatment for mild Alzheimer's disease, our ongoing Phase II clinical trial of ispronidine for AAMI, our planned Phase I and Phase II clinical trials of TC-2696, our ongoing Phase II clinical trial of Inversine as an add-on therapy in patients with major depressive disorder and the additional preclinical toxicology studies necessary to support an IND for clinical trials of TC-2216. We also expect that the net proceeds from this offering, together with our existing capital resources and payments that we expect to receive under our development agreement with The Stanley Medical Research Institute upon our achievement of specified milestones, will be sufficient to enable us to complete a Phase I clinical development program and a Phase II clinical trial of TC-1827 for cognitive impairment associated with schizophrenia. It is possible that we will not make the progress that we expect because the actual costs and timing of drug development, particularly clinical trials, are highly uncertain, are subject to substantial risk and often change depending on the target indication, the particular development strategy and the results of earlier clinical trials. As a result, we may need to raise additional funds from external sources to make the development progress described in this paragraph.

Until the funds are used as described above, we intend to invest the net proceeds from this offering in short-term interest-bearing, investment grade securities.

DIVIDEND POLICY

We have never declared or paid cash dividends on any of our shares of capital stock. We currently intend to retain future earnings, if any, to finance the expansion and growth of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors that our board of directors deems relevant. In addition, the terms of any future debt or credit facility may preclude us from paying dividends.

CAPITALIZATION

The following table sets forth our capitalization at September 30, 2004:

- on an actual basis;
- on a pro forma basis to give effect to the issuance of additional shares of our convertible preferred stock on December 6, 2004, the issuance of a convertible promissory note on December 15, 2004 and the conversion of all outstanding shares of our convertible preferred stock into 103,204,189 shares of common stock concurrently with the completion of this offering; and
- on a pro forma as adjusted basis to give further effect to:
 - our sale of _____ shares of common stock in this offering at an assumed initial public offering price of \$ _____ per share, after deducting estimated underwriting discounts and commissions and offering expenses payable by us;
 - our issuance of _____ shares of common stock upon the conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share; and
 - our issuance of _____ shares of common stock upon the exercise of an outstanding warrant concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share.

If the holder of the warrant instead exercises the warrant in full for cash, we would issue _____ shares of common stock for cash proceeds of approximately \$3.1 million. The cash exercise price of the warrant is \$ _____ per share.

You should read this table together with our financial statements and the related notes appearing at the end of this prospectus and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section and other financial information included in this prospectus.

| | As of September 30, 2004 | | |
|--|---|-----------|--------------------------|
| | Actual | Pro Forma | Pro Forma As Adjusted |
| | (unaudited) (in thousands, except share and per share data) | | |
| Total long-term obligations | \$ 2,553 | \$ 3,803 | \$ _____ |
| Redeemable convertible preferred stock, \$0.001 par value, 60,736,705 shares authorized, issued and outstanding actual; no shares authorized, issued or outstanding pro forma and pro forma as adjusted | 136,560 | — | |
| Stockholders’ equity (deficit): | | | |
| Common stock, \$0.001 par value, 85,000,000 shares authorized actual, 125,000,000 shares authorized pro forma and _____ shares authorized pro forma as adjusted; 1,887,356 issued and outstanding actual; _____ shares issued and outstanding pro forma; _____ shares issued and outstanding pro forma as adjusted | 2 | 105 | |
| Preferred stock, \$0.001 par value, no shares authorized, issued or outstanding actual and pro forma; _____ shares authorized and no shares issued and outstanding pro forma as adjusted | — | — | |
| Capital in excess of par value | 1,225 | 170,582 | |
| Common stock warrants | 214 | 214 | |
| Accumulated deficit | (117,835) | (117,835) | |
| Accumulated other comprehensive loss | — | — | |
| Total stockholders’ equity (deficit) | (116,394) | 53,066 | |
| Total capitalization | \$ 22,719 | \$ 56,869 | \$ _____ |

The table above does not include:

- 7,350,311 shares of common stock issuable upon exercise of options outstanding as of September 30, 2004, at a weighted average exercise price of \$0.64 per share, of which options to purchase 4,118,303 shares were exercisable; and
- 399,525 shares of common stock reserved for future grant under our 2000 equity incentive plan as of September 30, 2004.

DILUTION

If you invest in our common stock, your interest will be diluted immediately to the extent of the difference between the initial public offering price per share of our common stock and the pro forma net tangible book value of our common stock immediately after completion of this offering.

The historical net tangible book value of our common stock as of September 30, 2004 was approximately \$(116,954), or approximately \$(61.97) per share, based on 1,887,356 shares of common stock outstanding as of September 30, 2004. Historical net tangible book value per share represents our total tangible assets less total liabilities divided by the actual number of our common stock outstanding.

As of September 30, 2004, the pro forma net tangible book value of our common stock was approximately \$ _____ million, or approximately \$ _____ per share. Pro forma net tangible book value per share represents our total tangible assets less total liabilities divided by the pro forma number of shares of our common stock outstanding, after giving effect to a one-for-_____ reverse stock split of our common stock that will be effective prior to the completion of this offering, the issuance of additional shares of our convertible preferred stock on December 6, 2004, the conversion of all outstanding shares of our convertible preferred stock into 103,204,189 shares of common stock concurrently with the completion of this offering, the issuance of _____ shares of our common stock upon conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share and the issuance of 1,612,903 shares of common stock upon the exercise of an outstanding warrant in full for cash concurrently with the completion of this offering.

Assuming the sale of the shares of our common stock offered by this prospectus at an assumed initial public offering price of \$ _____ per share, after deducting estimated underwriting discounts and commissions and offering expenses payable by us, our pro forma net tangible book value as of September 30, 2004 would have been \$ _____, or \$ _____ per share. This represents an immediate increase in pro forma net tangible book value of \$ _____ per share to our existing stockholders and an immediate dilution in pro forma net tangible book value of \$ _____ per share to new investors purchasing in this offering at the initial public offering price. The following table illustrates this dilution on a per share basis:

| | |
|--|------------|
| Assumed initial public offering price per share | \$ _____ |
| Historical net tangible book value per share | \$ (61.97) |
| Increase attributable to the conversion of the convertible preferred stock | _____ |
| Pro forma net tangible book value per share before this offering | (_____) |
| Increase per share attributable to new investors | _____ |
| Pro forma net tangible book value per share after this offering | _____ |
| Dilution per share to new investors | \$ _____ |

The following table summarizes, on a pro forma basis as of September 30, 2004, the total number of shares of common stock purchased from us, the total consideration paid and the average price per share paid by existing stockholders and by new investors purchasing shares in this offering at an assumed initial public offering price of \$ _____ per share, before deducting estimated underwriting discounts and commissions and offering expenses payable by us.

| | Shares Purchased | | Total Consideration | | Average Price per Share |
|-----------------------|------------------|---------|---------------------|---------|-------------------------|
| | Number | Percent | Amount | Percent | |
| Existing stockholders | | % | \$ | % | \$ |
| New investors | | | | | |
| Total | | 100% | \$ | 100% | |

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The share data in the table above is based on shares outstanding as of September 30, 2004, counting as outstanding:

- 103,204,189 shares of common stock underlying all outstanding convertible preferred stock, including the additional shares of convertible preferred stock issued on December 6, 2004;
- _____ shares of common stock issuable upon conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share; and
- 1,612,903 shares of common stock issuable upon exercise of an outstanding warrant in full for cash concurrently with the completion of this offering.

The share data in the table above excludes:

- 7,350,311 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2004, at a weighted average exercise price of \$0.64 per share, of which options to purchase 4,118,303 shares were exercisable; and
- 399,525 shares of common stock reserved for future grant under our 2000 equity incentive plan as of September 30, 2004.

If the underwriters exercise their over-allotment in full, the following will occur:

- the number of shares of our common stock held by existing stockholders would decrease to approximately _____ % of the total number of shares of our common stock outstanding after this offering; and
- the number of shares of our common stock held by new investors would increase to _____ shares, or approximately _____ % of the total number of our common stock outstanding after this offering.

SELECTED FINANCIAL DATA

You should read the following selected financial data together with our financial statements and the related notes appearing at the end of this prospectus and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section and other financial data included in this prospectus.

We have derived the statement of operations data for the years ended December 31, 2001, 2002 and 2003 and the balance sheet data as of December 31, 2002 and 2003 from our audited financial statements included in this prospectus. We have derived the statement of operations data for the year ended December 31, 2000 and the balance sheet data as of December 31, 2000 and 2001 from our audited financial statements not included in this prospectus. We became an independent company in August 2000, prior to which we were a wholly owned subsidiary of R.J. Reynolds Tobacco Company. We have derived the statement of operations data for the year ended December 31, 1999 and the balance sheet data as of December 31, 1999 from our unaudited financial statements not included in this prospectus. We have derived the statement of operations data for the nine months ended September 30, 2003 and 2004 and the balance sheet data as of September 30, 2003 and 2004 from our unaudited financial statements included in this prospectus. In the opinion of our management, these unaudited financial statements reflect all adjustments, consisting only of normal recurring adjustments, necessary for a fair presentation of these financial statements. Our historical results for any prior or interim period are not necessarily indicative of the results to be expected for the fiscal year ending December 31, 2004 or for any other period.

The pro forma net loss attributable to common stockholders per share information is computed using the weighted average number of common shares outstanding, after giving pro forma effect to the conversion of all shares of our convertible preferred stock outstanding as of December 31, 2003 and September 30, 2004 into 73,739,905 shares of common stock concurrently with the completion of this offering, as if the conversion had occurred at the date of the original issuance. This pro forma information does not give effect to the issuance of additional shares of our convertible preferred stock on December 6, 2004, to the conversion of an outstanding convertible promissory note or to the exercise of an outstanding warrant.

| | Year ended December 31, | | | | | Nine months ended September 30, | |
|---|-------------------------|---|--------------------|--------------------|--------------------|------------------------------------|--------------------|
| | 1999 | 2000 | 2001 | 2002 | 2003 | 2003 | 2004 |
| | (unaudited) | (in thousands, except share and per share data) | | | | | (unaudited) |
| Statement of Operations Data: | | | | | | | |
| Net revenue | \$ 2,350 | \$ 2,351 | \$ 1,703 | \$ 2,286 | \$ 2,458 | \$ 1,816 | \$ 1,581 |
| Operating expenses: | | | | | | | |
| Research and development | 2,104 | 3,675 | 8,152 | 16,244 | 18,179 | 13,376 | 17,782 |
| General and administrative | 1,436 | 1,653 | 2,302 | 4,135 | 3,600 | 2,698 | 3,764 |
| Cost of product sales | — | — | — | 244 | 743 | 540 | 28 |
| Purchased in-process research and development | — | — | — | 2,666 | — | — | — |
| Total operating expenses | 3,540 | 5,328 | 10,454 | 23,289 | 22,522 | 16,614 | 21,574 |
| Loss from operations | (1,190) | (2,977) | (8,751) | (21,003) | (20,064) | (14,798) | (19,993) |
| Interest and dividend income | — | 536 | 1,449 | 88 | 791 | 546 | 356 |
| Interest expense | — | — | — | (103) | (122) | (96) | (96) |
| Loss on disposal of fixed assets | — | — | — | (54) | — | — | (4) |
| Net loss | (1,190) | (2,441) | (7,302) | (21,072) | (19,395) | (14,348) | (19,737) |
| Preferred stock accretion | — | (981) | (3,808) | (4,173) | (8,341) | (6,199) | (6,426) |
| Net loss attributable to common stockholders | \$ (1,190) | \$ (3,422) | \$ (11,110) | \$ (25,245) | \$ (27,736) | \$ (20,547) | \$ (26,163) |
| Basic and diluted net loss per share applicable to common stockholders | \$ (2,380.00) | \$ (30.58) | \$ (26.80) | \$ (45.28) | \$ (33.91) | \$ (27.04) | \$ (16.82) |
| Shares used to compute basic and diluted net loss per share | 500 | 111,915 | 414,624 | 557,492 | 817,894 | 759,937 | 1,555,090 |
| Pro forma basic and diluted net loss per share applicable to common stockholders (unaudited) | | | | | \$ (0.27) | | \$ (0.26) |
| Shares used to compute pro forma basic and diluted net loss per share (unaudited) | | | | | 71,118,629 | | 75,294,995 |

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| | As of December 31, | | | | | As of September 30, | |
|---|---|-----------|-----------|-----------|-----------|------------------------|-----------|
| | 1999 | 2000 | 2001 | 2002 | 2003 | 2003 | 2004 |
| | (unaudited) | | | | | (unaudited) | |
| | (in thousands, except share and per share data) | | | | | | |
| Balance Sheet Data: | | | | | | | |
| Cash, cash equivalents and short-term investments | \$ — | \$ 28,053 | \$ 21,180 | \$ 49,361 | \$ 42,977 | \$ 42,433 | \$ 24,425 |
| Working capital | 1,305 | 27,654 | 20,371 | 46,685 | 40,526 | 45,934 | 21,054 |
| Total assets | 1,804 | 29,338 | 24,396 | 54,379 | 47,390 | 51,966 | 29,208 |
| Long-term debt, net of current portion | — | — | — | 2,088 | 1,462 | 1,622 | 1,654 |
| Redeemable convertible preferred stock | — | 54,418 | 58,365 | 108,026 | 130,134 | 127,992 | 136,560 |
| Accumulated deficit | (6,335) | (27,581) | (38,691) | (63,936) | (91,672) | (84,515) | (117,835) |
| Total stockholders' equity (deficit) | 36 | (27,314) | (38,268) | (63,335) | (90,796) | (83,665) | (116,394) |

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing at the end of this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this prospectus for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company engaged in the design, discovery and development of a new class of drugs to treat multiple diseases and disorders by selectively targeting a class of receptors known as neuronal nicotinic acetylcholine receptors, or NNRs. We are developing our most advanced product candidates as treatments for target indications in three therapeutic areas: cognitive impairment, pain and depression. Within these areas, we have three product candidates in clinical development and three preclinical product candidates. We expect to advance one of our preclinical product candidates into clinical development in the first half of 2005. We also have multiple preclinical programs for target indications outside these areas in which we believe that NNRs can be exploited for medical benefit. We have worldwide commercialization rights for all of our product candidates. Inversine, our product candidate currently in a Phase II clinical trial as an add-on therapy in patients with major depressive disorder, is approved in the United States for moderately severe to severe essential hypertension. We believe that Inversine is the only FDA-approved product designed to target an NNR.

We trace our scientific lineage to a research program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and effects of nicotine in the body and the function of nicotinic acetylcholine receptors. We were incorporated in Delaware in 1997 as a wholly owned subsidiary of RJR. In August 2000, we became an independent company when we issued shares of our series B convertible preferred stock to outside investors.

We have devoted substantially all of our resources to the discovery and development of our product candidates and technologies, including the design, conduct and management of preclinical and clinical studies and related manufacturing, regulatory and clinical affairs, and intellectual property prosecution. Through 1998, we received all of our funding from RJR. At the end of 1998, we entered into a collaboration agreement with the predecessor company to Aventis Pharma SA. Aventis Pharma SA is now controlled by Sanofi-Aventis. We received an upfront license fee and research support payments under this agreement which, together with a modest amount of additional financial support from RJR, funded our activities through August 2000. Since August 2000, we have funded our operations primarily through the private placement of equity securities and, to a much lesser extent, through payments we received from our collaborators, equipment and building lease incentive financing, sales of our product Inversine and government grants.

We have never been profitable. As of September 30, 2004, we had an accumulated deficit of \$117.8 million. We expect to continue to incur substantial losses for the foreseeable future. We expect our research and development expenses to increase substantially following completion of this offering as we expand our clinical trial activity, as our product candidates advance through the development cycle and as we invest in additional product opportunities and research programs. We also expect our general and administrative expenses to increase substantially as we expand our infrastructure. Clinical trials and preclinical studies are time-consuming, expensive and may never yield a product that will generate revenue. A substantial portion of our revenue for the next several years will depend on our entering into new collaborations. Our revenue may vary substantially from quarter to quarter and year to year. We believe that period-to-period comparisons of our results of operations are not meaningful and should not be relied upon as indicative of our future performance.

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We currently have one product available in the market, Inversine. We acquired rights to Inversine in August 2002. Inversine is approved for the management of moderately severe to severe essential hypertension, a high blood pressure disorder with an unknown cause. However, we believe that Inversine is prescribed predominantly for the treatment of neuropsychiatric disorders, including Tourette's syndrome, autism and bipolar disorder, in children and adolescents at a lower dose than is used to treat hypertension. Sales of Inversine generated revenue of \$815,000 for the year ended December 31, 2003 and \$584,000 for the nine months ended September 30, 2004.

We have entered into two collaboration agreements with Aventis. One of those collaboration agreements with Aventis terminated on January 2, 2005. The other collaboration agreement with Aventis covers the research, development and commercialization of Aventis compounds for the treatment of Alzheimer's disease and other central nervous system diseases. As of September 30, 2004, we had received a total of \$8.1 million in upfront license fees and payments for research and development services under the two agreements. In addition to royalties on potential product sales, we could receive up to \$8.0 million under the continuing agreement upon the achievement of pre-commercialization development and regulatory milestones related to Alzheimer's disease and up to \$8.0 million for each other central nervous system disease upon the achievement of pre-commercialization development and regulatory milestones related to that disease. The achievement of these milestones is uncertain. We may not receive any of these amounts or we may receive only a portion of them. The research term of this agreement expired in December 2004, and Aventis has informed us that it does not intend to extend the research term. We are only eligible to receive future payments from Aventis for any compounds that are selected for further development within six months after the expiration of the research term.

In December 2004, we entered into a development agreement with The Stanley Medical Research Institute relating to the development of our compound TC-1827 for the treatment of the cognitive impairment associated with schizophrenia. Upon effectiveness of the agreement, The Stanley Medical Research Institute paid us \$1.25 million in return for our issuance of a convertible promissory note in an equal principal amount.

In January 2001, we entered into a collaboration agreement with Dr. Falk Pharma GmbH covering the development and commercialization of one of our compounds for the treatment of ulcerative colitis and other gastrointestinal and liver diseases. Upon effectiveness of the collaboration agreement, Dr. Falk Pharma paid us a \$1.0 million upfront license fee and purchased \$1.0 million of our common stock. We and Dr. Falk Pharma shared the development costs for the lead compound subject to the collaboration agreement. We and Dr. Falk Pharma have discontinued the development of the lead compound.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses. On an ongoing basis, we evaluate these estimates and judgments, including those described below. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. These estimates and assumptions form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results and experiences may differ materially from these estimates.

While our significant accounting policies are more fully described in Note 2 to our financial statements appearing at the end of this prospectus, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our reported financial results and affect the more significant judgments and estimates that we use in the preparation of our financial statements.

Revenue Recognition

Our collaboration agreements contain multiple elements, including non-refundable upfront license fees, research payments for ongoing research and development, payments associated with achieving development and regulatory milestones and royalties to be paid based on specified percentages of net product sales or net profits, if

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any. We consider a variety of factors in determining the appropriate method of revenue recognition under these arrangements such as whether the elements are separable, whether there are determinable fair values and whether there is a unique earnings process associated with a particular element of an agreement.

We recognize research fee revenue from research services performed under our collaboration agreements as work is performed. We defer upfront payments and amortize them over the estimated research and development period. All revenue that we have recognized to date under these collaborations, or under government grants, is non-refundable. We recognize revenue from milestones with substantive performance risk upon achievement of the milestone. We have not yet received payment of any such milestone-based revenues. We record product sales revenues when goods are shipped, at which point title has passed, and we establish an allowance for estimated returns at that time.

Accrued Expenses

As part of the process of preparing financial statements, we are required to estimate accrued expenses. This process involves communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. To date, we have not adjusted our estimate at any particular balance sheet date in any material amount. Examples of estimated accrued expenses include:

- fees paid to contract research organizations in connection with preclinical and toxicology studies and clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to contract manufacturers in connection with the production of clinical trial materials and Inversine; and
- professional service fees.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and clinical research organizations that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we will adjust the accrual accordingly. If we do not identify costs that we have begun to incur or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates.

Purchased In-process Research and Development Expense

We determine the amount of any acquired in-process research and development expense based on an analysis of the cash flows that we expect to be generated by products that may arise from in-process technologies that we have acquired. As part of this analysis, we review the project rights that we acquire to determine the stage of their development, the probability of demonstrating sufficient safety and efficacy in clinical trials to obtain regulatory approval and product specific risk factors inherent in the drug development process. The product specific risk factors that we review include the type of drug under development, the likelihood of regulatory approval, manufacturing process capability, scientific rationale, preclinical and clinical safety and efficacy data, target product profile and development plans. Different estimates and assumptions for any of these factors would, if changed, result in a different estimate of in-process research and development expense.

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In August 2002, we acquired from Layton Bioscience, Inc. marketing and trademark rights to Inversine and patent rights related to its active ingredient for cash consideration of \$3.5 million. In allocating the purchase price, including the amount of in-process research and development, we considered an appraisal prepared by an independent appraiser using established valuation techniques for the pharmaceutical industry. We allocated approximately \$2.7 million of the purchase price to in-process research and development, which we expensed in connection with the acquisition.

Stock-Based Compensation

We account for our employee stock-based compensation in accordance with Accounting Principles Board Opinion No. 25 and related interpretations, or APB 25. Under APB 25, we do not recognize compensation expense when we issue stock options to employees and non-employee directors, unless the exercise price is below the fair market value of the underlying common stock on the date of grant. We recognize this compensation expense over the vesting periods of the shares purchasable upon exercise of options. We recorded deferred stock-based compensation related to stock options granted to employees and directors of \$92,600 during 2001, \$129,700 during 2002 and \$65,300 during 2003. We amortize our deferred stock-based compensation on a straight-line basis over the related option vesting periods, which range from immediate vesting to four years.

As required by Statement of Financial Accounting Standards, or SFAS, No. 123, *Accounting for Stock-Based Compensation*, as amended by SFAS No. 148, *Accounting for Stock-Based Compensation—Transition and Disclosure*, our financial statement footnotes disclose on a pro forma basis the amount of compensation expense that we would have recorded had we applied the fair value option methodology described in SFAS 123. Had we recorded all of our stock-based compensation using the SFAS 123 fair value methodology, our compensation expense would have been approximately \$450,000 greater and our diluted net loss per share attributable to common stockholders would have been approximately \$0.55 greater in 2003. For more information, you should refer to Note 2 to our financial statements included at the end of this prospectus.

Financial Operations Overview

Revenue

Inversine is our only commercial product generating revenue. Sales of Inversine generated revenue of \$815,000 for the year ended December 31, 2003 and \$584,000 for the nine months ended September 30, 2004. We have entered into an exclusive distribution agreement with a third party for the distribution of Inversine. We do not have or use a sales force or actively promote Inversine. Accordingly, we do not anticipate any significant increase in Inversine sales. If any of the very limited number of physicians that most often prescribe Inversine were to cease to do so, revenue generated by Inversine sales would likely be substantially less. We have no other commercial products for sale and do not anticipate that we will have any other commercial products for sale for at least the next several years.

Other revenue has consisted primarily of amounts earned for providing research and development services under our two collaboration agreements with Aventis and non-refundable upfront license fees that we received in connection with our first agreement with Aventis and our collaboration agreement with Dr. Falk Pharma. We recognize these non-refundable upfront license fees over the estimated research period of each of these agreements. We received research support payments from Aventis of \$1.4 million for the year ended December 31, 2002, \$1.3 million for the year ended December 31, 2003 and \$209,000 for the nine months ended September 30, 2004. The research term of our one continuing agreement with Aventis ended in December 2004, and we do not expect to receive any future research support payments.

In 2003, we were awarded a cooperative agreement from the National Institute of Standards and Technology through its Advanced Technology Program. The terms of the agreement provide for us to receive up to \$1.9 million over a three-year period to help fund the development of sophisticated new computer simulation software designed to more accurately predict biological and toxicological effects of drugs. The agreement provides for reimbursement of costs that we incur to perform specified work that is designed to meet the objectives of the

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agreement. We recognize grant revenues as we perform the work and incur reimbursable costs. Funding for awards under this program is subject to the availability of funds as determined annually in the Federal appropriations process.

Research and Development Expense

Since our inception, we have focused our activities on our drug discovery and development programs. We expense research and development expenses as they are incurred. Research and development expenses represented approximately 78% of our total operating expenses for the year ended December 31, 2001, 81% for the year ended December 31, 2002, 81% for the year ended December 31, 2003 and 82% for the nine months ended September 30, 2004.

Research and development expenses include expenses associated with:

- the employment of personnel involved in our drug discovery and development activities;
- research and development facilities and equipment;
- the screening, identification and optimization of product candidates;
- the development and enhancement of Pentad;
- formulation and process synthesis;
- production of clinical materials, including fees paid to contract manufacturers;
- preclinical animal studies, including the costs to engage third-party research organizations;
- clinical trials, including fees paid to contract research organizations to monitor and oversee some of our trials;
- quality assurance activities;
- compliance with FDA regulatory requirements;
- purchased in-process research and development;
- consulting, license and sponsored research fees paid to third parties; and
- depreciation of capital assets used to develop our products.

We use our employee and infrastructure resources across several projects. Consistent with our focus on the development of a class of drugs with potential uses in multiple indications, many of our costs are not attributable to a specifically identified project. Instead, these costs are directed to broadly applicable research efforts. Accordingly, we do not account for internal research and development costs on a project-by-project basis. As a result, we cannot state precisely the total costs incurred for each of our clinical and preclinical projects on a project-by-project basis.

The following table shows, for the periods presented, total payments that we made to third parties for preclinical study support, clinical supplies and clinical trial services for ispronnicline and TC-2696:

| Product Candidate | Year ended December 31, | | | Nine months ended September 30, |
|-------------------|-------------------------|-------|----------------|---------------------------------|
| | 2001 | 2002 | 2003 | 2004 |
| | | | (in thousands) | |
| Ispronnicline | \$— | \$976 | \$3,557 | \$ 3,175 |
| TC-2696 | — | — | 893 | 1,000 |
| Total: | \$— | \$976 | \$4,450 | \$ 4,175 |

At the end of 2004, we discontinued the development of two product candidates following the completion of Phase II clinical trials. We made total payments to third parties of \$922,000 for the year ended December 31, 2001, \$2.7 million for the year ended December 31, 2002, \$2.1 million for the year ended December 31, 2003 and \$4.1 million for the nine months ended September 30, 2004 in connection with these discontinued programs.

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We expect to continue to incur substantial research and development expenses for the foreseeable future. We anticipate that these expenses will increase substantially in 2005 and in subsequent years as we continue to advance our clinical stage product candidates through the development process, to advance additional product candidates into clinical trials and to invest in promising product opportunities in our research programs.

Our expenditures on current and future preclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. We test compounds in numerous preclinical studies for safety, toxicology and efficacy. We then conduct clinical trials for those product candidates that we determine to be the most promising. If we do not establish a collaboration covering the development of a particular product candidate, we fund these trials ourselves. As we obtain results from clinical trials, we may elect to discontinue or delay trials for some product candidates in order to focus our resources on more promising product candidates. Completion of clinical trials by us or our collaborators may take several years or more, but the length of time generally varies substantially according to the type, complexity, novelty and intended use of a product candidate. The cost of clinical trials may vary significantly over the life of a project as a result of a variety of factors, including:

- the number of patients who participate in the trials;
- the number of sites included in the trials;
- the length of time required to enroll trial participants;
- the duration of patient follow-up;
- the costs of producing supplies of the product candidates needed for clinical trials and regulatory submissions;
- the efficacy and safety profile of the product candidate; and
- the costs and timing of, and the ability to secure, regulatory approvals.

We have not received FDA or foreign regulatory marketing approval for any of our product candidates that are in development. In order to achieve marketing approval, the FDA or foreign regulatory agencies must conclude that our or our collaborators' clinical data establishes the safety and efficacy of the product candidates. Furthermore, our strategy includes entering into collaborations with third parties to participate in the development and commercialization of some of our product candidates. In situations in which third parties have control over the preclinical development or clinical trial process for a product candidate, the estimated completion date is largely under control of that third party and not under our control. We cannot forecast with any degree of certainty which of our product candidates will be subject to future collaborations or how such arrangements would affect our development plans or capital requirements.

As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenues from the commercialization and sale of any of our development stage product candidates.

General and Administrative Expense

General and administrative expense consists principally of salaries and other related costs for personnel in executive, finance, accounting, business development, information technology and human resource functions. Other general and administrative expenses include facility costs not otherwise included in research and development expense, patent related costs, and professional fees for consulting, legal and accounting services. We expect that general and administrative expense will increase during 2004 and subsequent years due to increased payroll, expanded infrastructure, increased consulting, legal, accounting and investor relations expenses associated with being a public company and costs incurred to secure collaborations with respect to any of our product candidates.

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Cost of Product Sales

Cost of product sales are those costs related directly to the sale of Inversine and are principally comprised of cost of goods sold, FDA product license fees, distribution expenses, product royalty obligations and product liability insurance.

Purchased In-process Research and Development Expense

Purchased in-process research and development expense consists of an allocated portion of the purchase price for the marketing rights to Inversine and related assets that we acquired in August 2002. We expensed the entire allocated portion as of the date of acquisition. We have not recorded purchased in-process research and development expense in any period other than 2002.

Interest and Dividend Income

Interest and dividend income consists of interest and dividends earned on our cash, cash equivalents and short-term investments.

Interest Expense

Interest expense consists of interest incurred to finance equipment, office furniture and fixtures.

Income Taxes

We have incurred net operating losses since our incorporation in 1997 and consequently have not paid federal, state or foreign income taxes in any period. We had net operating loss carryforwards of approximately \$57.5 million as of September 30, 2004 and \$46.1 million as of December 31, 2004. Utilization of the net operating loss carryforwards and credits may be subject to a substantial annual limitation due to ownership change limitations provided by Section 382 of the Internal Revenue Code of 1986, as amended, and similar state provisions. As a result of a series of stock issuances, we had such an ownership change on November 30, 2002 and we could experience additional ownership changes as a result of this offering or in the future. When an ownership change, as defined by Section 382, occurs, an annual limitation is imposed on a company's use of net operating loss and credit carryforwards attributable to periods before the change. For financial reporting purposes, we have recorded a valuation allowance to fully offset the deferred tax asset related to these carryforwards because realization of the benefit was uncertain.

Results of Operations

Nine Months ended September 30, 2004 and 2003

Revenue. We recognized revenue of \$1.6 million for the nine months ended September 30, 2004 compared to \$1.8 million for the corresponding period in 2003. The decrease resulted from a decrease of \$756,000 in research fee revenue generated from our collaboration agreement with Aventis relating to Aventis compounds, resulting from less activity under that agreement in 2004 as we progressed in late 2003 towards completion of the research requested by Aventis. We expect research fee revenues derived from that collaboration agreement in the fourth quarter of 2004 to decrease similarly as compared to the comparable period in 2003. The research term of that collaboration agreement expired on December 31, 2004. The decrease was partially offset by \$585,000 of grant revenue recognized in the first nine months of 2004, compared to \$67,000 recognized during the corresponding period in 2003. These grant revenues were derived from work performed under a cooperative agreement awarded to us in 2003 by the National Institute of Standards and Technology through its Advanced Technology Program to fund the development of sophisticated molecular simulation software. Inversine sales increased to \$584,000 for the first nine months of 2004 compared to \$582,000 for the corresponding period in 2003. We began selling Inversine in December 2002. In the fourth quarter of 2004, we will recognize the remaining \$825,000 of deferred revenue related to our collaboration agreement with Aventis that terminated on January 2, 2005.

Research and Development Expense. Research and development expense increased by \$4.4 million, or 33%, to \$17.8 million for the nine months ended September 30, 2004, from \$13.4 million for the corresponding

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period in 2003. The increase was primarily attributable to the costs associated with having four product candidates in clinical trials in the first nine months of 2004, compared to only two product candidates in clinical trials in the corresponding period of 2003. During the nine months ended September 30, 2004, we estimate that approximately 18% of our total research and development expenses were payments made to third parties in connection with our ispronicline program for conditions marked by cognitive impairment that afflict the elderly, 6% were payments made to third parties in connection with our TC-2696 program for pain and 23% were made to third parties in connection with the two discontinued clinical development programs. We spent the remaining 53% of our total research and development expenses on salaries, benefits, and infrastructure costs associated with our internal research and development capabilities, including clinical programs, preclinical programs and research efforts, and on payments to third parties in connection with preclinical programs.

General and Administrative Expense. General and administrative expense increased by \$1.1 million, or 39%, to \$3.8 million for the nine-month period ended September 30, 2004, from \$2.7 million for the corresponding period in 2003. This increase resulted from our investment in development of the administrative infrastructure necessary to enable us to expand our operations, to support our development efforts and to fulfill the additional reporting and regulatory requirements applicable to a public company. The increase was principally attributable to increased expenses of \$443,000 related to expansion of our business development staff and an increase in spending on business development pursuits, \$266,000 of additional patent related expenses and increases in our legal and other professional fees.

Cost of Product Sales. Cost of product sales for the nine months ended September 30, 2004 was \$28,000 compared to \$540,000 for the corresponding period in 2003. All of these costs related to sales of Inversine. The decrease in cost of product sales of \$512,000 resulted from a successful outcome in 2004 of our request for a waiver of FDA product and establishment fees that had been assessed by FDA in 2003 and 2002. In July 2004, the FDA informed us that our fee waiver request had been granted in full. We had accrued the costs for these FDA fees in our financial statements since our acquisition of Inversine in August 2002, as there was no assurance that our fee waiver request would be granted.

Interest and Dividend Income. Interest and dividend income decreased by \$190,000 to \$356,000 for the nine months ended September 30, 2004, from \$546,000 for the corresponding period in 2003. The decrease was primarily attributable to lower levels of cash and short-term investments.

Interest Expense. Interest expense was \$96,000 for the nine months ended September 30, 2004, unchanged from the corresponding period in 2003.

Years ended December 31, 2003 and 2002

Revenue. Revenue increased to \$2.5 million for the year ended December 31, 2003 from \$2.3 million for 2002. The increase resulted primarily from the inclusion of a full year of Inversine sales in 2003 of \$815,000, compared to a partial year of Inversine sales in 2002 of \$243,000. We began selling Inversine in December 2002. License fee revenues decreased to \$270,000 in 2003 from \$635,000 in 2002 primarily as a result of revisions to the estimated research terms used as the basis for revenue recognition of the non-refundable upfront license fees that we received in our collaborations with Aventis and Dr. Falk Pharma.

Research and Development Expense. Research and development expense increased by \$2.0 million, or 12%, to \$18.2 million for the year ended December 31, 2003, from \$16.2 million for 2002. The increase resulted principally from increased spending of \$2.9 million on our later stage clinical programs and increased personnel and infrastructure costs of \$539,000 associated with the expansion of our internal clinical development and regulatory affairs capabilities. This was offset in part by a decrease of \$1.8 million resulting from the conclusion in 2002 of a program to screen several of our preclinical candidates to select those to advance into clinical trials. During the year ended December 31, 2003, we estimate that approximately 20% of our total research and development expenses were payments made to third parties in connection with our ispronicline program for conditions marked by cognitive impairment that afflict the elderly, 5% were payments made to third parties

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in connection with our TC-2696 program for pain and 12% were made to third parties in connection with the two discontinued clinical development programs. We spent the remaining 63% of our total research and development expense on salaries, benefits, and infrastructure costs associated with our internal research and development capabilities, including clinical programs, preclinical programs and research efforts, and on payments to third parties in connection with preclinical programs.

General and Administrative Expense. General and administrative expense decreased by \$536,000, or 13%, to \$3.6 million for the year ended December 31, 2003, from \$4.1 million for 2002. This decrease resulted principally from a decrease of \$330,000 from the costs incurred in 2002 associated with our relocation to a new leased facility, severance costs of \$257,000 and a reduction in patent related costs in 2003 compared to 2002. In 2003 we increased our spending on the development of the administrative infrastructure necessary to enable us to expand our operations, support our development efforts and facilitate the additional reporting and regulatory requirements related to becoming a public company.

Cost of Product Sales. Cost of product sales increased to \$743,000 for the year ended December 31, 2003, from \$244,000 for 2002. The increase in cost of product sales for 2003 resulted primarily from increased sales of Inversine.

Interest and Dividend Income. Interest and dividend income increased by \$703,000 to \$791,000 for the year ended December 31, 2003, from \$88,000 for 2002. The increase resulted from substantially higher average cash balances during 2003 as a result of the funds we received from the sale of shares of our series C convertible preferred stock. We raised \$45.5 million in this financing in November 2002 and \$13.8 million in March 2003.

Interest Expense. Interest expense was \$123,000 for the year ended December 31, 2003 compared to \$103,000 for 2002.

Years ended December 31, 2002 and December 31, 2001

Revenue. Revenue increased to \$2.3 million for the year ended December 31, 2002 from \$1.7 million for 2001. The increase resulted principally from an increase of \$289,000 in research fee revenue generated from our Aventis collaboration as a result of higher levels of research activity and Inversine sales of \$243,000 in December 2002 when we began selling the product.

Research and Development Expense. Research and development expense increased by \$8.0 million, or 98%, to \$16.2 million for the year ended December 31, 2002, from \$8.2 million for 2001. The increase resulted principally from \$1.8 million in costs attributable to a program to screen several of our preclinical candidates to ascertain those to advance into clinical trials, increased spending of \$1.7 million to fund third-party services in connection with a clinical development program that we are no longer pursuing, and \$1.0 million for preclinical studies, toxicology and regulatory expenses directed towards advancing ispronidine into clinical trials. We also incurred increased salary and benefits costs as we expanded our product development capabilities with the hiring of experienced key personnel. In addition, we incurred increased infrastructure costs in connection with our relocation in March 2002 to a new leased facility which includes expanded lab and research space. This also resulted in higher depreciation charges associated with the new equipment and furnishings that we acquired.

General and Administrative Expense. General and administrative expense increased by \$1.8 million, or 80%, to \$4.1 million for the year ended December 31, 2002, from \$2.3 million for 2001. This increase resulted from our investment in the administrative infrastructure necessary to enable us to expand our operations, to support our development efforts and to attract and hire members of executive management. In the first quarter of 2002, we relocated our operations to a new leased facility. The costs of the relocation were approximately \$330,000, and the new facility increased our occupancy related costs in 2002 by \$661,000 compared to 2001. Salary and benefits expenses increased by \$498,000, which included the costs associated with the addition of a chief financial officer in the first quarter of 2002 and severance costs. In 2002 we also increased our spending on professional fees related to business development, legal and public relations services.

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Cost of Product Sales. Cost of product sales for the year ended December 31, 2002 was \$244,000. All of these sales related to Inversine, which we began selling in December 2002. We had no cost of product sales expenses for the year ended December 31, 2001.

Interest and Dividend Income. Interest and dividend income decreased by \$1.4 million to \$88,000 for the year ended December 31, 2002. The decrease resulted from substantially lower average cash balances during 2002 compared to 2001 and lower interest rates during the year.

Interest Expense. Interest expense was \$103,000 for the year ended December 31, 2002. The interest expense related to outstanding indebtedness on a loan facility established to finance equipment and other fixed assets. We had no interest expense for the year ended December 31, 2001.

Liquidity and Capital Resources

Sources of Liquidity

Since we became an independent company in 2000, we have financed our operations and internal growth primarily through private placements of convertible preferred stock. As of September 30, 2004, we had derived aggregate net proceeds of \$88.4 million from these private placements. In December 2004, we completed an additional private placement of convertible preferred stock from which we derived aggregate net proceeds of \$32.9 million. We have received additional funding from upfront license fees and payments for research and development services under collaboration agreements, equipment and building lease incentive financing, government grants and interest income. As of September 30, 2004, we have received \$10.0 million under our collaboration agreements. As of December 31, 2004, we are no longer conducting research under our collaboration agreements for which we would receive any research support payments. We also received loan proceeds of \$1.25 million in December 2004 from The Stanley Medical Research Institute in connection with a development agreement relating to the development of our compound TC-1827 for the treatment of the cognitive impairment associated with schizophrenia. We began generating revenues from product sales of Inversine in December 2002. To date, the net contribution of Inversine sales have not been a significant source of cash and we do not expect them to be a significant source in the future.

Our cash, cash equivalents and short-term investments were \$24.4 million as of September 30, 2004, \$43.0 million as of December 31, 2003 and \$49.4 million as of December 31, 2002. As noted above, in December 2004, we completed an additional private placement of convertible preferred stock from which we derived aggregate net proceeds of \$32.9 million.

Cash Flows

Net cash used for operating activities was \$18.8 million for the nine months ended September 30, 2004, reflecting a net loss of \$19.7 million offset primarily by an increase of \$1.0 million in accounts payable and accrued expenses resulting from increased commitments related to our clinical trials. Net cash used for operating activities was \$19.3 million for the year ended December 31, 2003, primarily reflecting a net loss occurring for this period of \$19.4 million. Net cash used for operating activities was \$17.1 million for the year ended December 31, 2002, reflecting a net loss of \$21.1 million partially offset by non-cash charges for acquired in-process research and development of \$2.7 million and depreciation and amortization of \$1.0 million. Accounts payable and accrued expenses increased by \$1.5 million as of December 31, 2002, compared to December 31, 2001 primarily as a result of an increase in outsourced development activities with contract research organizations.

Net cash used in investing activities was \$556,000 for the nine months ended September 30, 2004, and \$545,000 for the year ended December 31, 2003. These amounts exclude cash flows from the purchase and sale of investments and were primarily to purchase equipment for use in expanding our internal research and development activities. Investing activities for the year ended December 31, 2002, exclusive of cash flows from the purchase and sale of investments, included the use of \$1.3 million for the purchase of equipment and furniture, the use of \$3.5 million for the purchase of the marketing rights to Inversine and related assets from Layton Bioscience, Inc. and the receipt of a \$2.0 million rent incentive from the owner of our facilities in connection with our entering into a lease with a minimum five-year term.

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Net cash used in financing activities was \$1.0 million for the nine months ended September 30, 2004. As of September 30, 2004, we had borrowing capacity of \$1.0 million available under our equipment financing loan facility. We borrowed \$1.0 million under the facility in April 2004 to finance equipment that we had previously purchased. Net cash provided by financing activities for the year ended December 31, 2003 was \$13.4 million and consisted principally of net proceeds of \$13.8 million from the issuance of shares of our series C convertible preferred stock, and proceeds of \$239,000 received in connection with the purchase of our common stock upon the exercise of stock options, partially offset by \$637,000 of principal repayments on equipment financing. Net cash provided by financing activities for the year ended December 31, 2002 was \$48.2 million and consisted principally of net proceeds of \$45.5 million from the issuance of shares of our series C convertible preferred stock and proceeds of \$3.0 million from long-term debt, comprised of a \$2.5 million equipment financing loan repayable over 48 months and a \$500,000 incentive loan from the City of Winston-Salem which requires no repayments and carries no interest charges for the initial five years, partially offset by \$325,000 of equipment financing principal repayments.

In May 2002, we borrowed \$2.5 million from R.J. Reynolds Tobacco Holdings, Inc. to finance equipment and other fixed assets that we had previously purchased. The borrowing bears a fixed interest rate of 6.6%, is payable in 48 equal monthly installments and matures in May 2006. In January 2004, we amended the terms of our loan facility to permit us to borrow up to an additional \$2.0 million in 2004 in up to three separate borrowings. Each borrowing would bear a fixed interest rate equal to a theoretical four-year U.S. Treasury Rate on the disbursement date plus 3.5%, be payable in 48 equal monthly installments and be secured by specified tangible fixed assets determined sufficient by the lender at the time of disbursement. We borrowed \$1.0 million in April 2004 and \$973,000 in December 2004 under the amended loan facility to finance equipment. The April 2004 borrowing bears a fixed interest rate of 5.9%, is payable in 48 equal monthly installments and matures in April 2008. The December 2004 borrowing bears a fixed interest rate of 6.9%, is payable in 48 monthly installments and matures in January 2009. All borrowings under the loan facility are secured by specified tangible fixed assets. As of December 31, 2004, the outstanding principal balance under the loan facility was \$2.8 million.

On December 6, 2004, we sold 27,272,728 shares of convertible preferred stock to 11 of our existing stockholders for net proceeds of \$32.9 million.

On December 15, 2004, we entered into a development agreement with The Stanley Medical Research Institute, a nonprofit organization that supports the research and development of treatments for schizophrenia. In connection with this agreement, we issued a \$1.25 million convertible promissory note to The Stanley Medical Research Institute. The note bears interest at 10% per annum and matures on January 1, 2007. However, if not earlier paid, the outstanding principal and accrued interest under the note will automatically convert into shares of our common stock concurrently with the completion of this offering at a conversion price equal to the initial public offering price.

Funding Requirements

We have incurred significant losses since our inception. As of September 30, 2004, we had an accumulated deficit of \$117.8 million. We expect to continue to incur substantial operating losses for the foreseeable future. Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the scope, progress, results and cost of preclinical development and laboratory testing and clinical trials;
- the costs, timing and outcome of regulatory review;
- the number and characteristics of product candidates that we pursue;
- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims;
- the costs of establishing sales and marketing functions and of establishing arrangements for manufacturing;
- the rate of technological advancements for the indications that we target;

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- our ability to establish strategic collaborations and licensing or other arrangements on terms favorable to us;
- the costs to satisfy our obligations under existing and potential future collaborations;
- the timing, receipt and amount of sales or royalties, if any, from our potential products; and
- the extent and scope of our general and administrative expenses.

Although we currently have not specifically identified any material commitments for capital expenditures, we anticipate that implementing our strategy will require substantial increases in our capital expenditures and other capital commitments as we expand our clinical trial activity, as our product candidates advance through the development cycle, and as we invest in additional product opportunities and research programs and expand our infrastructure. We do not expect our existing capital resources and the net proceeds from this offering to be sufficient to enable us to fund the completion of the development of any of our product candidates. We expect that our existing capital resources, together with the net proceeds from this offering, will be sufficient to fund our operations through the end of 2006. However, our operating plan may change as a result of many factors, including those described above, and we may need additional funds sooner than planned to meet operational needs and capital requirements for product development.

We do not expect to generate sufficient cash from our operations to sustain our business for the foreseeable future. Unless we are able to do so, we expect our continuing operating losses to result in increases in our cash used in operations over the next several quarters and years. To the extent our capital resources are insufficient to meet future capital requirements, we will need to finance future cash needs through public or private equity offerings, debt financings or corporate collaboration and licensing arrangements. Additional equity or debt financing, or corporate collaboration and licensing arrangements, may not be available on acceptable terms, if at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate our research and development programs, reduce our planned commercialization efforts, or obtain funds through arrangements with collaborators or others that may require us to relinquish rights to certain drug candidates that we might otherwise seek to develop or commercialize independently. Additionally, any future equity funding may dilute the ownership of our equity investors.

We cannot estimate the completion dates and costs of our current internal research and development programs due to inherent uncertainties in outcomes of clinical trials and regulatory approvals of our product candidates. We cannot be certain that we will be able to successfully complete our research and development projects or successfully find collaboration or distribution partners for our product candidates. Our failure to complete our research and development projects could have a material adverse effect on our financial position or results of operations.

To date, inflation has not had a material effect on our business.

Contractual Obligations

The following table summarizes our significant contractual obligations and commercial commitments as of December 31, 2003:

| Contractual Obligations | Payments due by period (in thousands) | | | | |
|-------------------------------|--|----------------|-----------------|-----------------|---------------|
| | Total | 2004 | 2005-2007 | 2008-2009 | After 2009 |
| Long-term debt | \$ 2,038 | \$ 576 | \$ 962 | \$ 163 | \$ 337 |
| Operating leases | 5,216 | 1,456 | 2,911 | 849 | — |
| Other contractual obligations | 4,220 | 3,984 | 230 | 6 | — |
| Total | \$11,474 | \$6,016 | \$ 4,103 | \$ 1,018 | \$ 337 |

The amounts reflected in the above table do not include contingent payments for milestones and royalties on potential product sales that we may become obligated to make under technology license agreements to which we are a party. The amounts of long-term debt reflected in the above table include both principal and interest payments. The amounts of long-term debt reflected in the above table do not include the \$1.25 million

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convertible promissory note that we issued on December 15, 2004. If not earlier paid, the outstanding principal and accrued interest under that note will automatically convert into shares of our common stock concurrently with the completion of this offering. The amounts of long-term debt reflected in the above table also do not include \$1.0 million that we borrowed in April 2004 and \$973,000 that we borrowed in December 2004 under our amended loan facility with R.J. Reynolds Tobacco Holdings, Inc.

Quantitative and Qualitative Disclosures about Market Risk

The primary objective of our investment activities is to preserve our capital to fund operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of cash equivalents and short-term investments in a variety of securities of high credit quality. As of September 30, 2004, we had cash, cash equivalents and short-term investments of \$24.4 million consisting of cash and highly liquid investments deposited in a highly rated financial institution in the United States. A portion of our investments may be subject to interest rate risk and could fall in value if market interest rates increase. However, because our investments are short-term in duration, we believe that our exposure to interest rate risk is not significant and a 1% movement in market interest rates would not have a significant impact on the total value of our portfolio. We actively monitor changes in interest rates. We adjusted our portfolio in April 2004 to eliminate positions in investments that were subject to potentially significant interest rate risks.

We contract for the conduct of certain of our clinical trials and other research and development and manufacturing activities with contract research organizations, investigational sites and manufacturers in Europe. We may be subject to exposure to fluctuations in foreign exchange rates in connection with these agreements. We do not hedge our foreign currency exposures. We have not used derivative financial instruments for speculation or trading purposes.

Recent Accounting Pronouncements

During 2003, the Financial Accounting Standards Board, or the FASB, issued Interpretation No. 46, *Consolidation of Variable Interest Entities*, or FIN 46, which is an interpretation of Accounting Research Bulletin No. 51, *Consolidated Financial Statements*. FIN 46 requires that, if an entity has a controlling interest in a variable interest entity, the assets, liabilities and results of activities of the variable interest entity should be included in the consolidated financial statements of the entity. FIN 46 is effective immediately for all new variable interest entities created or acquired after January 31, 2003. For variable interest entities created or acquired prior to February 1, 2003, the provisions of FIN 46 must be applied in the first interim or annual period beginning after June 15, 2003. We implemented the provisions of FIN 46 for our financial statements for the year ended December 31, 2003. We have no investment in or contractual relationship or other business relationship with a variable interest entity. Therefore, the adoption of FIN 46 did not affect our financial position or results of operations.

In May 2003, the FASB issued SFAS No. 150, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity*. SFAS 150 establishes how a company classifies and measures certain financial instruments with characteristics of both liabilities and equity, including redeemable convertible preferred stock. SFAS 150 is effective for financial instruments entered into or modified after May 31, 2003 and otherwise effective at the beginning of the interim period commencing July 1, 2003, except for mandatory redeemable financial instruments of nonpublic companies. The adoption of SFAS 150 did not affect our financial position or results of operations.

In October 2004, the FASB announced that FASB Statement No. 123R, *Share-Based Payment*, which would require all companies to measure compensation cost for all share-based payments, including employee stock options, at fair value, would be effective for public companies for interim or annual periods beginning after June 15, 2005. SFAS 123R would require companies to expense the fair value of all stock options that have future vesting provisions, are modified or are newly granted beginning on the grant date of such options. We will evaluate the requirements of the final standard, which is expected to be issued in December 2004, to determine the impact on our financial position and results of operations.

BUSINESS

Overview

We are a biopharmaceutical company engaged in the design, discovery and development of a new class of drugs to treat multiple diseases and disorders of the central nervous system by selectively targeting neuronal nicotinic acetylcholine receptors, or NNRs. NNRs are found on nerve cells throughout the nervous system and serve as key regulators of nervous system activity. We trace our scientific lineage to a research program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and effects of nicotine, a compound that interacts non-selectively with all nicotinic acetylcholine receptors. Since that time, we have developed a deep understanding of the biological characteristics and functions of NNRs and have learned that compounds that interact with NNRs have the potential to achieve positive medical effects by modulating their activity. We have built an extensive patent estate covering the structure or therapeutic use of small molecules designed to regulate the central nervous system by selectively affecting specific NNR subtypes.

We are developing our most advanced product candidates as treatments for target indications in three therapeutic areas: cognitive impairment, pain and depression. Within these areas, we have three product candidates in clinical development and three preclinical product candidates. We expect to advance one of our preclinical product candidates into clinical development in the first half of 2005. We also have multiple preclinical programs for target indications outside these areas in which we believe that NNRs can be exploited for medical benefit. We have worldwide commercialization rights for all of our product candidates. Our most advanced product candidates are:

Cognitive Impairment

- **Ispronicline (TC-1734).** Ispronicline is a novel small molecule that we are developing as an oral treatment for conditions marked by cognitive impairment that afflict the elderly, including Alzheimer's disease and age associated memory impairment, commonly referred to as AAMI. In 2004, we completed two Phase II clinical trials of ispronicline, one in AAMI and one in mild cognitive impairment, commonly referred to as MCI. We began screening subjects for a separate Phase II clinical trial of ispronicline in AAMI in the fourth quarter of 2004. We plan to initiate two Phase II clinical trials of ispronicline in Alzheimer's disease in 2005. We expect the first of these trials, which we plan to initiate in mid-2005, to assess ispronicline as a stand-alone treatment for mild Alzheimer's disease. We expect the second of these trials, which we plan to initiate in the second half of 2005, to assess ispronicline as a complementary, or add-on, therapy to a currently approved treatment for mild to moderate Alzheimer's disease. We are also evaluating potential additional clinical development of ispronicline for indications such as cognitive impairment associated with schizophrenia, cognitive impairment following coronary artery bypass grafting, MCI, attention deficit hyperactivity disorder and various forms of dementia.
- **TC-1827.** TC-1827 is a novel small molecule that we are developing as an oral treatment for cognitive impairment associated with schizophrenia under a development agreement that we entered into in December 2004 with The Stanley Medical Research Institute. TC-1827 is currently a preclinical product candidate. We plan to file an investigational new drug application, or IND, and initiate a Phase I clinical trial of TC-1827 in the first half of 2005.

Pain

- **TC-2696.** TC-2696 is a novel small molecule that we are developing as an oral treatment for acute post-operative pain. Depending on clinical trial results, available resources and other considerations, we may pursue development of TC-2696 for other classes of pain as well. In 2004, we completed a Phase I clinical trial of TC-2696. We plan to initiate a Phase I multiple rising dose clinical trial to further assess the safety and tolerability profile of TC-2696 in the second quarter of 2005. If the results of that trial are favorable, we plan to initiate a Phase II clinical trial of TC-2696 in hysterectomy or molar extraction patients in the first half of 2006.

Depression

- ***Inversine and TC-5214.*** We began screening patients for a Phase II clinical trial of our product Inversine as an add-on therapy in patients with major depressive disorder in January 2005. Inversine, which we believe is the only FDA-approved product designed to target an NNR, is approved in the United States for the management of moderately severe to severe essential hypertension, a high blood pressure disorder with an unknown origin. However, we believe that Inversine is prescribed predominantly for the treatment of neuropsychiatric disorders, including Tourette's syndrome, autism and bipolar disorder, in children and adolescents at a lower dose than is used to treat hypertension. TC-5214 is one of the molecular components of mecamylamine hydrochloride, the active ingredient in Inversine. TC-5214 is currently a preclinical product candidate. We are evaluating the development of TC-5214 as an add-on therapy for depression.
- ***TC-2216.*** TC-2216 is a novel small molecule that we are developing as an oral treatment for depression and anxiety disorders. TC-2216 is currently a preclinical product candidate. In 2005, we plan to conduct the additional preclinical toxicology studies necessary to support an IND for clinical trials of TC-2216.

In addition, we have preclinical research programs in schizophrenia, smoking cessation and obesity.

We develop product candidates using our proprietary databases and computer-based molecular design technologies, which we refer to collectively as Pentad. Pentad relies on extensive biological data for a library of diverse compounds that we have developed and gathered over 20 years. Together with our proprietary assays and novel screening methods, Pentad enables us to efficiently identify, prioritize, characterize and optimize novel compounds designed to selectively target specific NNR subtypes in an effort to achieve desired results and limit or potentially eliminate adverse side effects. We used Pentad to design or optimize ispronidine, TC-1827, TC-2696 and TC-2216.

Role of NNRs in the Nervous System

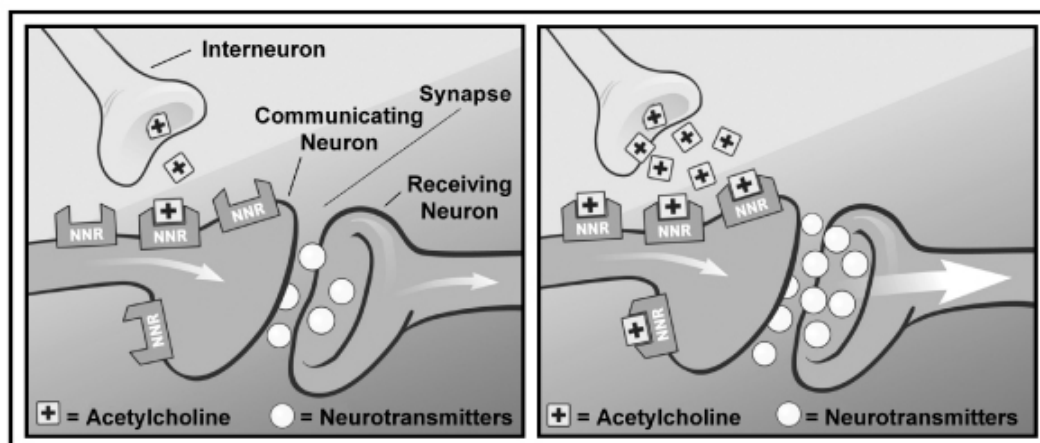
The human nervous system is a massive communications network that sends and receives information throughout the body via billions of specialized nerve cells known as neurons. Neurons continually gather information about the body's internal and external environment and send signals to the brain. These signals pass from one neuron to another when electrical impulses of a communicating neuron are converted into chemicals called neurotransmitters. This occurs at the gap between a communicating neuron and a receiving neuron known as a synapse. When released by a communicating neuron, neurotransmitters bind to specialized proteins known as receptors located across the synapse on the receiving neuron to enable the signal to continue. The major neurotransmitters in the brain are dopamine, serotonin, norepinephrine, glutamate, gamma-aminobutyric acid, or GABA, and acetylcholine.

NNRs are a class of receptors found in the nervous system that play a critical role in modulating the release of neurotransmitters to regulate nervous system activity. When the neurotransmitter acetylcholine is released from a nearby neuron, called an interneuron, and binds to an NNR on a communicating neuron, the flow of neurotransmitters from the communicating neuron to a receiving neuron is adjusted by the NNR. This action, known as neuromodulation, results in a greater release of neurotransmitters across the synapse when the nervous system is understimulated and a lesser release of neurotransmitters across the synapse when the nervous system is overstimulated. As neuromodulators, NNRs serve as the nervous system's self-adjusting "volume knob."

The nervous system will not operate properly if the relative levels of key neurotransmitters in the brain are not maintained in a normal balance. A disruption in this balance can cause many common nervous system diseases and disorders. We believe that compounds that target NNRs to trigger their activity can be used to treat these diseases and disorders.

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The following diagrams illustrate the role of NNRs in neuromodulation. In the illustration on the left, the release of a limited amount of acetylcholine from the interneuron causes the NNRs to release a limited amount of neurotransmitters across the synapse. In the illustration on the right, the release of more acetylcholine from the interneuron causes the NNRs to release a greater amount of neurotransmitters.



NNRs are comprised of five protein subunits that are arranged like staves of a barrel around a central pore. Each different combination of five subunits represents an NNR subtype. There are several subtypes, each of which is identified by Greek letters. Scientific evidence has established that individual NNR subtypes have particular functions in the body that are relevant to a number of debilitating diseases and disorders, as set forth below.

| NNR Subtype | Primary Functions Impacted | Diseases or Disorders Potentially Implicated |
|-------------------|------------------------------|---|
| $\alpha 7$ | sensory gating; cognition | schizophrenia; cognitive impairment |
| $\alpha 4\beta 2$ | cognition pain perception | Alzheimer's disease; AAMI; MCI; ADHD acute, chronic and neuropathic pain |
| $\alpha 6\beta 3$ | motor control | Parkinson's disease |

Our scientists and their former colleagues at R.J. Reynolds Tobacco Company have played a prominent role in the growth of knowledge about NNRs, as well as the effects of compounds that mimic the action of acetylcholine and interact with different NNR subtypes. For example, we believe that nicotine's well-documented abilities to enhance attention, learning and memory result primarily from its interaction with the $\alpha 4\beta 2$ NNR and with the $\alpha 7$ NNR in the brain. Many published studies evaluating the effects of nicotine in humans and animals, as well as published studies showing the prevalence of diseases such as Alzheimer's disease and Parkinson's disease in non-smokers as compared to smokers, suggest the therapeutic effects of compounds such as nicotine that interact with NNRs. However, despite their positive effects, these compounds have historically not been desirable as therapies because they have not been sufficiently selective. This means that these compounds interact not only with NNRs, but also with nicotinic acetylcholine receptors in the muscles and ganglia that are associated with adverse effects such as increased heart rate, high blood pressure, irregular heartbeat, nausea, vomiting and a dangerous slowing of breathing known as respiratory depression.

Based on our years of focus on NNRs and the expertise we have built over that time, we are developing product candidates that are designed to interact selectively with specific NNR subtypes to promote positive medical effects and limit or potentially eliminate adverse side effects.

Our Business Strategy

Our goal is to become a leader in the discovery, development and commercialization of novel drugs that selectively target NNRs in order to treat diseases and disorders where there is significant medical need and commercial potential. To achieve this goal, we are pursuing the following strategies:

- *Develop and commercialize drugs that selectively target specific NNR subtypes.* Based on our understanding of the role of NNRs in the nervous system, we believe that drugs designed to selectively target specific NNR subtypes can have positive medical effects with limited or no adverse side effects. We use our scientific expertise and Pentad to identify compounds that selectively target specific NNR subtypes as potential treatments for diseases and disorders of the central nervous system.
- *Remain at the forefront of the commercialization of NNR research.* We have established ourselves as a leader in NNR research over the last 20 years. Our scientists and their former colleagues at RJR have published more than 150 NNR-related articles in leading scientific journals and more than 200 abstracts. Our leadership position in this area is also reflected in our extensive patent estate that includes 85 issued or pending United States patents and patent applications and numerous foreign counterparts. We intend to continue to invest significant resources to build upon our NNR expertise and to expand our intellectual property portfolio. We augment our own research by collaborating with commercial and academic institutions that seek access to our proprietary knowledge and compounds.
- *Identify and prioritize indications in which drugs that selectively target specific NNR subtypes can be exploited for medical benefit.* We have identified numerous indications in which NNRs have been implicated and for which we believe that drugs that selectively target specific NNR subtypes can provide a medical benefit. We prioritize our product development opportunities in an effort to sustain our product pipeline for indications in which there is a significant medical need and commercial potential.
- *Collaborate selectively to develop and commercialize product candidates.* We intend to selectively enter into collaboration agreements with leading pharmaceutical and biotechnology companies to assist us in furthering the development of our product candidates. In particular, we intend to enter into these third-party arrangements for target indications in which our potential collaborator has particular expertise or that involve a large, primary care market that must be served by large sales and marketing organizations. In entering into these collaboration agreements, our goal will be to maintain co-promotion or co-commercialization rights in the United States and, in some cases, other markets.
- *Build a specialized sales and marketing organization.* We intend to build an internal sales and marketing organization for target indications in which specialists heavily influence the market, particularly neurology and psychiatry. We believe that we can effectively serve these markets with a specialized sales force, enabling us to retain greater value from our product candidates that receive marketing approval than if we relied on a third party's sales force.

Opportunities in Our Target Indications

Because NNRs are so widespread in the body, we believe that there are a number of areas in which compounds that target NNRs could provide a therapeutic benefit, including:

- diseases and disorders of the central nervous system, commonly referred to as the CNS;
- smoking cessation;
- obesity; and
- inflammation.

Our primary product development focus is on diseases and disorders of the CNS, which represent a major segment of the global healthcare environment. The Business Insights Healthcare Report published in association with Reuters estimated the total worldwide CNS pharmaceutical market to be \$63.3 billion in 2003. Three of the top ten selling drugs in the world in 2003, Pfizer's Zoloft, Eli Lilly's Zyprexa and GlaxoSmithKline's Paxil/Seroxat, treat diseases and disorders of the CNS. However, despite their commercial success, many current CNS drugs are only moderately effective or are accompanied by significant side effects or other drawbacks. Accordingly, we believe that substantial opportunities exist for new therapies that address CNS diseases and disorders. We are currently conducting clinical development of ispronicline for AAMI and TC-2696 for acute post-operative pain. We are also currently conducting a clinical trial of Inversine in patients with major depressive disorder. We plan to commence clinical trials of ispronicline for Alzheimer's disease and of TC-1827 for cognitive impairment associated with schizophrenia in 2005.

Cognitive Impairment in the Elderly

Cognition refers to a collection of mental processes that enable the acquisition, storage, retrieval and use of information. Cognitive functions such as attention, learning and memory underlie fundamental day-to-day activities. Impairment of these functions can impact an individual's ability to function effectively and, in severe cases, to maintain quality of life. Cognitive impairment is particularly prominent in the growing elderly population. The most severe form of cognitive impairment is dementia, which can render a person unable to care for himself or herself. The most common form of dementia in the elderly is Alzheimer's disease. Cognitive impairment without dementia ranges in severity from age associated memory impairment, commonly known as AAMI, to mild cognitive impairment, commonly known as MCI. Researchers have estimated that between 10% and 15% of persons with MCI are diagnosed with Alzheimer's disease each year. In addition, 80% of persons with MCI who participated in a third-party study were diagnosed with Alzheimer's disease within six years of being diagnosed with MCI.

Alzheimer's disease is a debilitating brain disorder for which there is no cure. The disease progresses in stages from mild to moderate to severe and gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. Mild Alzheimer's disease is characterized by mild forgetfulness and difficulty acquiring basic information and communicating. Patients generally exhibit the symptoms of mild Alzheimer's disease for two to four years before progressing to the moderate stage. Moderate Alzheimer's disease is characterized by forgetfulness, failure to recognize friends and family, disorientation regarding time and place and personality changes. Patients generally exhibit the symptoms of moderate Alzheimer's disease for up to ten years before progressing to the severe stage. Severe Alzheimer's disease is characterized by difficulty performing simple tasks and activities associated with daily living. Patients with severe Alzheimer's disease require continuous care and generally do not survive for more than three years.

The Business Insights Healthcare Report estimates that Alzheimer's disease affects approximately 13.5 million people in the world's seven major pharmaceutical markets, which are the United States, France, Germany, Italy, Spain, the United Kingdom and Japan, including approximately 4.5 million people in the United States. That report notes that epidemiological studies indicate that an estimated 5% of persons over age 65 and an estimated 24% of persons over age 85 suffer from the disease. Espicom Business Intelligence, a provider of business information for the pharmaceutical and other industries, estimates that the worldwide market for Alzheimer's disease therapies was approximately \$2.6 billion in 2003.

The term AAMI describes a common condition characterized by gradual memory loss or other cognitive impairment that generally occurs with normal aging. A person who is at least 50 years of age and scores at least one standard deviation below the mean established for young adults on a standardized memory test without evidence of dementia, neurological illness or other medical cause may be classified with AAMI. AAMI is not currently listed in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, or DSM-IV, the manual published by the American Psychiatric Association to establish diagnostic criteria. However, DSM-IV does list the term "age related cognitive decline," which is often used by the medical community interchangeably with AAMI,

as an “objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person’s age.” Although estimates of the prevalence of AAMI in the elderly vary greatly because of varying methodologies and definitions of AAMI, one published study indicates that AAMI may affect as many as 38% of people over age 65. Based on a 2000 report of the Federal Interagency Forum on Aging-Related Statistics, this represents over 13 million people in the United States alone. The Federal Interagency Forum report projects that the number of people in the United States age 65 or older will double by 2030.

The treatment of Alzheimer’s disease is currently dominated by a class of drugs called acetylcholinesterase inhibitors, which includes Aricept, Reminyl and Exelon. The treatment most recently approved by the FDA is Namenda, which has a different mechanism of action than acetylcholinesterase inhibitors and is the only product approved for the treatment of severe Alzheimer’s disease. There is currently no product approved by the FDA for the treatment of AAMI. We believe that, when AAMI is treated at all, physicians typically prescribe acetylcholinesterase inhibitors. We believe that acetylcholinesterase inhibitors have limitations in that only about half of Alzheimer’s disease patients who take them show symptomatic improvement and they do not substantially delay the progressive deterioration and death of cells in the brain that can lead to more severe impairment and debilitation.

Cognitive Impairment Associated with Schizophrenia

Schizophrenia is a chronic, severe and disabling form of psychosis. The disease is characterized by symptoms such as delusions, hallucinations, the inability to disregard familiar stimuli, sometimes referred to as sensory gating, disorganized speech, grossly disorganized or catatonic behavior and prolonged loss of emotion, feeling, volition or drive. In addition, schizophrenia is often marked by impairment in cognitive functions, such as attention, vigilance, memory, and reasoning, that plays a primary role in the inability of schizophrenic patients to function normally.

The Business Insights Healthcare Report estimates that schizophrenia affects over 9 million people in the world’s seven major pharmaceutical markets, including approximately 3.7 million people in the United States. Scientists have estimated that up to 75% of schizophrenic patients are cognitively impaired. The Business Insights Healthcare Report estimates that the worldwide market for schizophrenia therapies was approximately \$9.7 billion in 2003.

Traditional treatments for schizophrenia are not effective to treat cognitive impairment associated with schizophrenia. While it has been reported that more recently developed treatments for schizophrenia, known as “atypical anti-psychotics,” may have some effect on cognitive impairment, there is little evidence that the effect is lasting and leads to an improvement in daily functioning. Also, atypical anti-psychotics may cause agranulocytosis, an acute disease characterized by significant loss of white blood cells that prevent infection, as well as agitation, anxiety, muscle tremor, drowsiness, dizziness, headache, insomnia, weight gain and diabetes. There are currently no drugs approved for cognitive impairment associated with schizophrenia.

Pain

There are two general categories of pain, nociceptive and neuropathic. Pain occurs when base nerve endings known as pain receptors are activated and a pain signal is transmitted through the nervous system to the brain. With nociceptive pain, the pain signal starts with damage to tissue and is typically accompanied by inflammation. With neuropathic pain, the pain signal results from inflammation of the peripheral nerves or other injury to the nervous system itself. A common form of neuropathic pain is sciatica, which is characterized by compression of the sciatic nerve resulting in leg and back pain. Neuropathic pain also arises from diabetes, cancer and exposure to chemotherapy or radiation. Both nociceptive and neuropathic pain can be either acute or chronic.

According to the Business Insights Healthcare Report, the worldwide market for pain therapies was approximately \$20 billion in 2003. That report estimates that approximately 80 million people in the world’s seven major pharmaceutical markets suffer annually from acute nociceptive pain following a surgical procedure. Datamonitor, another provider of business information for the pharmaceutical and other industries, estimates that 39 million people worldwide suffer annually from some form of neuropathic pain.

There is no single product available to treat all types of pain, and we believe that there are limitations to the existing treatments for each individual type of pain. Acute pain is typically treated with a class of drugs known as opioids such as morphine. Prolonged use of opioids, however, may result in a tolerance to the drug, ultimately making it ineffective. In addition, the use of opioids can result in addiction and abuse. As a result, physicians are often reluctant to prescribe opioids for an extended period of time or at all. Chronic pain is most often treated with a class of drugs known as non-steroidal anti-inflammatory drugs. These drugs are often not sufficiently effective. In a nationwide survey of over 1,000 adults conducted in the United States in August 2003, only 58% of chronic pain sufferers rated their prescription medications as very or somewhat effective. No class of drugs, including opioids and non-steroidal anti-inflammatory drugs, has demonstrated consistent effectiveness in treating neuropathic pain.

Depression

Depression is a severe psychiatric mood disorder. It is characterized by a wide range of symptoms that cause significant impairment in daily functioning, such as persistent despondence, loss of interest in normal activities, changes in appetite, difficulty in sleeping, agitation, apathy or feelings of guilt. The most common forms of depression are major depressive disorder and dysthymia, which is less severe.

Datamonitor estimates that depression affects nearly 36 million people in the seven major pharmaceutical markets, including approximately 13 million people in the United States. Espicom Business Intelligence estimates that the worldwide market for depression therapies was approximately \$14.8 billion in 2003.

Depression is thought to be associated with the disruption and imbalance in the brain of the neurotransmitters dopamine, norepinephrine and serotonin. Medications currently used to treat depression, such as selective serotonin reuptake inhibitors, dual uptake inhibitors, and tricyclics, are designed to increase the levels of one or more of those neurotransmitters. However, these drugs may take two to four weeks to be effective, if at all, and may cause side effects like nausea, increased sweating, fatigue and sexual dysfunction that are experienced before any benefit. Moreover, experts have estimated that approximately 20% to 30% of patients with depression do not respond to anti-depressant medications.

Our Product Development Pipeline

We are developing our most advanced product candidates as treatments for target indications in three therapeutic areas: cognitive impairment, pain and depression. Within these areas, we have three product candidates in clinical development and three preclinical product candidates. We expect to advance one of our preclinical product candidates into clinical development in the first half of 2005. We also have multiple preclinical programs for target indications outside of these areas in which we believe that NNRs can be exploited for medical benefit. We have worldwide commercialization rights for all of our product candidates. Inversine, our product candidate currently in a Phase II clinical trial as an add-on therapy in patients with major depressive disorder, is approved in the United States for the management of moderately severe to severe essential hypertension. Except for Inversine for the treatment of hypertension, neither the FDA nor any foreign regulatory authority has approved any of our product candidates for marketing.

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The following table summarizes our product development pipeline.

| <u>Area of Therapeutic Focus</u> | <u>Product Candidate</u> | <u>Target Indication</u> | <u>Status of Development</u> |
|----------------------------------|--------------------------|--|--|
| Cognitive Impairment | Ispronicle (TC-1734) | Alzheimer's disease | Phase II trial in MCI complete; two Phase II trials in Alzheimer's disease planned, one for initiation in mid-2005 and one for initiation in the second half of 2005 |
| | | AAMI | Initial Phase II trial complete; separate Phase II trial ongoing |
| | TC-1827 | Cognitive impairment associated with schizophrenia | Preclinical; filing of IND and Phase I trial planned for initiation in the first half of 2005 |
| Pain | TC-2696 | Acute post-operative pain | Initial Phase I trial complete; separate Phase I trial planned for initiation in the second quarter of 2005 |
| Depression | Inversine | Major depressive disorder | Phase II trial ongoing |
| | TC-5214 | Depression | Preclinical |
| | TC-2216 | Depression and anxiety disorders | Preclinical |

We are currently conducting our Phase II clinical trial of ispronicle in the United States and we have previously conducted two Phase II clinical trials of ispronicle in the United Kingdom. We conducted our initial Phase I clinical trial of TC-2696 in France. We are currently screening patients for our Phase II clinical trial of Inversine in the United States. We plan to conduct a portion of this trial in India if we receive approval of a regulatory filing comparable to an IND that we have submitted.

Cognitive Impairment

We are developing two product candidates for conditions marked by cognitive impairment. We are developing ispronicle for conditions that afflict the elderly, including Alzheimer's disease and AAMI. We are developing TC-1827 for cognitive impairment associated with schizophrenia.

Ispronicle

Ispronicle (TC-1734) is a novel small molecule that we are developing as an oral treatment for conditions marked by cognitive impairment that afflict the elderly, including Alzheimer's disease and AAMI. In the fourth quarter of 2004, we began screening subjects for a Phase II clinical trial of ispronicle in AAMI. Earlier in 2004, we completed a Phase II clinical trial of ispronicle in 76 elderly persons with AAMI and a Phase II clinical trial in 40 elderly persons classified with MCI, a condition marked by cognitive impairment that is more severe than AAMI but less severe than Alzheimer's disease. We had previously evaluated ispronicle in 84 healthy volunteers in four Phase I clinical trials.

While the exact causes of Alzheimer's disease, AAMI and MCI are unknown, the aging process is generally accompanied by a decline of cognitive function linked to a progressive deterioration and death of cells in the brain. This is known as neurodegeneration. If neurodegeneration reaches a more advanced stage, such as in Alzheimer's disease, a person becomes debilitated and unable to care for himself or herself. In addition, published third-party studies have shown that patients with Alzheimer's disease have deficient levels of acetylcholine and other key neurotransmitters in the brain. We believe that these neurotransmitter levels are also deficient, perhaps to a lesser degree, in persons with AAMI and MCI.

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Published third-party studies have shown a reduced number of $\alpha 4\beta 2$ NNRs in persons with dementia, suggesting the involvement of $\alpha 4\beta 2$ in cognition. In our preclinical animal studies, ispronicline triggered activity of $\alpha 4\beta 2$, enhanced the release of acetylcholine, enhanced memory and showed meaningful separation between the doses at which positive effects on memory and side effects were first seen. In two preclinical in vitro studies that we conducted, ispronicline protected neuronal cells from deterioration and death, a process known as neuroprotection. Based on these results and published studies that link neuroprotection to exposure to nicotine, a non-selective activator of all NNRs with particularly strong activity at $\alpha 4\beta 2$, we believe that ispronicline has the potential to prevent or delay neurodegeneration.

In other published third-party studies, nicotine administered by injection or by patch improved attention and learning in Alzheimer's disease patients. In addition, studies have shown that Alzheimer's disease is more prevalent in non-smokers than in smokers. We believe these studies suggest the potential of drugs that target NNRs to treat Alzheimer's disease.

In addition to Alzheimer's disease and AAMI, we are evaluating potential additional clinical development of ispronicline for indications such as cognitive impairment associated with schizophrenia, cognitive impairment following coronary artery bypass grafting, MCI, attention deficit hyperactivity disorder and various forms of dementia.

Clinical Development of Ispronicline

Phase I Clinical Trials. During 2003, we completed four Phase I clinical trials of ispronicline in 84 healthy volunteers in which the compound was well tolerated. The results of these trials are summarized below.

- In a single rising dose trial with 48 volunteers, the compound was well tolerated in doses of up to 320mg. We also observed an acceleration in brainwaves thought to be associated with positive effects on attention, suggesting that the compound had reached the brain.
- In a multiple rising dose trial with 24 volunteers, 50mg, 100mg and 200mg doses of ispronicline were administered over a 10-day period. We observed a dose-dependent positive effect on attention at the end of the trial measured by the ability of the volunteers to focus on a particular task to the exclusion of other tasks.
- In a pharmacokinetic trial, six elderly volunteers were given a single 80mg dose to assess the compound's absorption, distribution, metabolism and excretion. We observed positive effects on memory and learning, including improved episodic memory based on word recall and picture recognition assessments. These effects lasted up to 48 hours after a single oral dose.
- In a food interaction trial, six volunteers were administered an 80mg dose with or without having eaten and the compound was well tolerated.

Phase II Clinical Trials. In the fourth quarter of 2004, we completed a double blind, placebo-controlled Phase II clinical trial of ispronicline in 76 elderly persons classified with AAMI. We conducted the trial at multiple sites in the United Kingdom under a clinical trial exemption, the United Kingdom equivalent to an IND. The primary objective of this trial was to assess the safety and tolerability of ispronicline in elderly subjects compared to placebo. The secondary objectives of this trial were to assess the efficacy of ispronicline in improving cognitive function and changes in mood state.

In 2004, we also completed a double blind, placebo-controlled clinical trial of ispronicline in 40 elderly volunteers classified with MCI. This trial had similar objectives to the AAMI trial and was also conducted in the United Kingdom.

In the AAMI trial, the subjects were divided into four dose groups – 20 subjects in the 50mg group, 20 subjects in the 100mg group, 20 subjects in the 125mg dose group and 16 subjects in the 150mg group. In the MCI trial, the subjects were divided into 50mg and 100mg dose groups of 20 subjects each. In both trials, each

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subject was initially dosed either with the applicable dose of ispronicline or a placebo daily over a three-week period. Then, after a two-week period without being dosed, each subject was changed to be dosed with either a placebo or ispronicline, as the case may be, daily for another three-week period. Each subject took ispronicline or a placebo before eating on the day of dosing. During the trials, routine safety measures were recorded and pharmacokinetic assessments were made for each subject. In addition, subjects were assessed for changes in cognitive function and mood state before and after dosing on the first day of the three-week dosing period and then again on the last day of the dosing period. The trials were double blind, meaning that neither the subjects nor the clinical investigators knew during the trials which subjects were receiving TC-1734 and which were receiving the placebo.

In the 50mg, 100mg and 125mg arms of the AAMI trial, ispronicline was well tolerated, with no serious adverse events reported. In the 150mg dose group, three out of eight subjects treated with ispronicline experienced side effects such as headache, lightheadedness, dizziness and vomiting and dropped out of the trial. Because of these side effects, we ceased dosing new subjects at 150mg.

We used a computer-based test battery developed by CDR Ltd. in the AAMI and MCI trials to test for changes in cognitive function. This test battery includes measures of attention, speed of cognitive processes and memory that assess the ability to react to stimuli, recognize words and pictures and recall words. These measures are then used to make composite assessments on the following five factors:

- power of attention, which assesses the intensity of concentration;
- continuity of attention, which assesses the ability to sustain concentration;
- working memory, or short-term memory, which assesses the ability to retain for a short period of time information that has not been previously learned;
- episodic memory, or long-term memory, which assesses the ability to store, hold for an extended period of time and retrieve information of an episodic nature, such as an event, name, object, scene or appointment; and
- speed of memory, which assesses the time it takes to recall an item from memory.

CDR has indicated that its battery has been used to assess cognitive performance in over 500 clinical trials worldwide. We also used the CDR test battery in our Phase I clinical trials of ispronicline. We selected it because of its comprehensive measures and CDR's extensive database of test results in unimpaired persons that enable assessment of clinical relevance.

Compared to subjects that received placebo, subjects in the 50mg dose group that received ispronicline showed improvements on four of the five factors: power of attention; continuity of attention; episodic memory and speed of memory. These results were statistically significant. A clinical trial result is statistically significant if it is unlikely to have occurred by chance. The statistical significance of clinical trial results is determined by a widely used statistical method that establishes the p-value of the results. Under this method, a p-value of 0.05 or less represents statistical significance. In the 50mg dose group, the power of attention factor had a p-value of 0.020, the continuity of attention factor had a p-value of 0.043, the episodic memory factor had a p-value of 0.010, and the speed of memory factor had a p-value of 0.008. These effects were consistent with the effects seen in our Phase I trials.

The positive effects that we observed in the 50mg dose group were less pronounced in the other dose groups. In the 100mg dose group, we observed improvements on three of the factors. The results on the power of attention factor, with a p-value of 0.049, and the episodic memory factor, with a p-value of 0.022, were statistically significant. The other factor on which we observed improvement in the 100mg dose group was speed of memory, which had a p-value of 0.090. In the 125mg dose group, we observed improvements on two of the factors. The result on the working memory factor, with a p-value of 0.038, was statistically significant. The other factor on which we observed improvement in the 125mg dose group was episodic memory, which had a p-value of 0.078. For those subjects in the 150mg dose group who completed the trial, improvements were shown on four of the factors. The

results on the continuity of attention factor, with a p-value of 0.049, and the speed of memory factor, with a p-value of 0.018, were statistically significant. The other factors on which we observed improvement in the 150mg dose group were power of attention, with a p-value of 0.088, and working memory, with a p-value of 0.094. The results of the AAMI trial suggest that ispronicline is well tolerated at a dose range of up to 125mg, that 150mg is the maximum tolerated dose of ispronicline for this trial design and that the compound had positive effects on cognition at all tolerated doses tested.

To generate additional data related to the tolerability of ispronicline, we also tested eight elderly persons classified with AAMI at a dose of 150mg, after having eaten, using the same trial design. This enabled us to assess the impact of food on the tolerability of ispronicline by comparing it in subjects dosed at 150mg who had eaten and in subjects dosed at 150mg who had not eaten. As we expected, the results indicated that the 150mg dose of ispronicline was better tolerated in subjects who had eaten than in subjects who had not eaten. All but one of the subjects in the dose group who had eaten completed the trial, and we observed no serious adverse events. In addition, improvements were shown in this dose group on three of the CDR factors. The results on the continuity of attention factor, with a p-value of 0.029, and the speed of memory factor, with a p-value of 0.036, were statistically significant. The other factor on which we observed improvement in this dose group was episodic memory, which had a p-value of 0.079.

As in the AAMI trial, ispronicline was well tolerated in the MCI trial, with only one serious adverse event reported. A subject who had a history of an abnormally slow heart rate lost consciousness and was hospitalized approximately one-and-one-half weeks following the end of the dosing phase of the trial. We do not believe that this adverse event was related to ispronicline. Subjects in the 100mg dose group of the trial showed improvements on four of the CDR factors. The results on the power of attention factor, with a p-value of 0.042, and the episodic memory factor, with a p-value of 0.044, were statistically significant. The other factors on which we observed improvement in the 100mg dose group were working memory, with a p-value of 0.070, and speed of memory, with a p-value of 0.100. Subjects in the 50mg dose group of the trial did not show improvement.

Plans for Future Development in Alzheimer's Disease. We believe that the positive effects that we observed on the cognitive measures assessed in our completed Phase II clinical trials of ispronicline indicate that ispronicline has the potential to be an effective treatment for Alzheimer's disease, both as a stand-alone treatment and as an add-on therapy. Our belief is based in part on the results of our Phase II clinical trial of ispronicline in persons with MCI and the suspected relationship between MCI and Alzheimer's disease. Researchers have estimated that between 10% and 15% of persons with MCI are diagnosed with Alzheimer's disease each year. In addition, 80% of persons with MCI who participated in a third-party study were diagnosed with Alzheimer's disease within six years of being diagnosed with MCI. These data suggest that there may be a disease progression from MCI to Alzheimer's disease. Moreover, scientists have suggested that episodic memory is the earliest deficit that an Alzheimer's disease patient suffers. Published third-party studies have shown that tests that assess episodic memory best distinguish persons with Alzheimer's disease from unimpaired elderly persons. As described above, we observed positive effects on the episodic memory factor in both of our previous Phase II clinical trials of ispronicline in persons with AAMI and MCI.

We plan to initiate a double-blind, placebo controlled Phase II clinical trial of ispronicline for the treatment of mild Alzheimer's disease in mid-2005. We expect to include in the trial approximately 250 patients who were recently diagnosed with Alzheimer's disease for the first time, who have not previously taken medication for Alzheimer's disease and who score within specified ranges on the Mini-Mental Status Exam and the global Clinical Dementia Rating scale, standardized tests often used to characterize the severity of Alzheimer's disease. The co-primary outcome measures of the trial will be an updated 13-item version of the Alzheimer's Disease Assessment Scale-cognitive subscale, or ADAS-Cog, the measure most often used to assess the efficacy of drugs for Alzheimer's disease, and a subject global improvement scale. The updated version of ADAS-Cog contains three more items than the original version of ADAS-Cog. The additional three items are designed to enhance the sensitivity of the measure for evaluation of less impaired patients. We also plan to include a cognitive test battery in the trial as a secondary measure.

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In addition, we plan to initiate a double-blind, placebo controlled Phase II clinical trial of ispronicline as an add-on therapy to a currently approved treatment for mild to moderate Alzheimer's disease in the second half of 2005. We expect to include in this trial approximately 450 patients who have previously been diagnosed with Alzheimer's disease and have been taking a stable dose of the approved treatment for between six and 18 months. The co-primary outcome measures of the trial will be the original version of ADAS-Cog and the Clinician's Interview Based Impression of Change, which is a commonly used rating scale in which the investigator makes a global assessment of change in an Alzheimer's disease patient's condition based on clinical interviews of the patient, information provided by patient's caregiver and any testing of the patient that has been conducted.

Plans for Future Development in AAMI. In the fourth quarter of 2004, we began screening subjects for a Phase II clinical trial to assess the efficacy of ispronicline in AAMI. The trial is designed to provide additional evidence that ispronicline improves cognitive performance in cognitively impaired elderly persons. We are conducting the trial at multiple sites in the United States. The trial design provides for 174 subjects with AAMI to be dosed once daily for 16 weeks with either ispronicline or a placebo. Those subjects dosed with ispronicline will receive 25mg for the first two weeks of the dosing phase, 37.5mg for the next two weeks and 50mg for the remaining 12 weeks. There are three co-primary efficacy endpoints for the trial:

- improvement on the power of attention factor of the CDR test battery as compared to placebo;
- improvement on the episodic memory factor of the CDR test battery as compared to placebo; and
- improvement in subject global impression, a standard seven-point overall cognitive improvement scale in which each subject rates himself on attention, memory and speed of thinking.

In addition, we will assess each subject's change from baseline on a number of other tests and scales as secondary endpoints. Also, to obtain additional information regarding the correlation between the amount of ispronicline present in the body and the compound's effects, we will make pharmacokinetic assessments at various points during the trial.

In a recent letter that we received from the FDA in response to our submission of the protocol for our ongoing Phase II trial of ispronicline for the treatment of AAMI, the FDA informed us that it believes it is questionable whether AAMI satisfies the criteria necessary for AAMI to be recognized as a distinct clinical condition. However, we believe that the results of our Phase II clinical trials of ispronicline in AAMI and MCI and the neuroprotective effect that we observed in preclinical in vitro studies of ispronicline suggest the potential of ispronicline as an early treatment for progressive cognitive impairment. Based on feedback that we have received from researchers whom we believe to be leaders in this medical area and our belief that acceptance of the possibility and viability of a treatment for cognitive impairment associated with normal aging is emerging in the medical community, we believe that AAMI is an indication that the FDA may be willing to recognize in the future. While our Phase II clinical trial for AAMI is ongoing, we plan to consult with the FDA regarding the potential of AAMI as a distinct clinical condition for which the FDA would approve a drug. Based on the results of our Phase II AAMI trial and our planned consultation with the FDA, we will evaluate the continued clinical development of ispronicline for the treatment of AAMI. Even if the FDA were to be unwilling to recognize AAMI as a distinct clinical condition, we believe that our ongoing Phase II AAMI trial, if successful, would benefit us in our efforts to gain marketing approval of ispronicline for Alzheimer's disease by further establishing the safety profile of ispronicline and further demonstrating its cognitive effects in an expanded number of cognitively impaired elderly persons.

Additional Clinical Support. We are developing a salt form of ispronicline that is different from the salt form that we used in our completed trials, that we are currently using in our ongoing Phase II trial in AAMI and that we plan to use in our Phase II trial in mild Alzheimer's disease. We believe that the new salt form will cost less to make than the current salt form. We also believe that the new salt form will be more soluble than the current salt form, which could result in an improved pharmacokinetic profile. We plan to initiate a bioequivalence study designed to determine the dose of the new salt necessary to achieve the presence in the blood of the same amount of ispronicline as specified doses of the current salt in the second quarter of 2005. The

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study will include between six and eight healthy volunteers. We anticipate that we will use the new salt form of ispronicline in our Phase II trial of ispronicline as an add-on therapy for Alzheimer's disease that we plan to initiate in the second half of 2005 and in future clinical trials of ispronicline.

In addition, we plan to initiate a clinical trial designed to determine the extent of any interaction between ispronicline and donepezil hydrochloride, which is marketed as Aricept and currently the leading treatment for mild to moderate Alzheimer's disease, in the second quarter of 2005. The trial will include between six and eight healthy volunteers. In the trial, we will assess the amounts of ispronicline and donepezil in the blood and make routine safety assessments. We will select the approved treatment with which we will conduct our planned Phase II clinical trial of ispronicline as an add-on therapy for Alzheimer's disease based in part on the results of this trial.

TC-1827

TC-1827 is a novel small molecule that we are developing as an oral treatment for cognitive impairment associated with schizophrenia under a development agreement that we entered into in December 2004 with The Stanley Medical Research Institute. We plan to file an IND and commence a Phase I clinical trial of TC-1827 in the first half of 2005.

In our preclinical in vitro studies, we found TC-1827 to be a potent activator of the $\alpha 4\beta 2$ NNR and to avoid interaction with nicotinic acetylcholine receptors in the muscles and ganglia that are associated with side effects. Published third-party studies in humans and animals have shown that compounds that act on $\alpha 4\beta 2$ have positive effects on cognition.

In our preclinical animal studies conducted under our terminated collaboration agreement with Aventis, TC-1827 demonstrated improvement in a variety of cognitive measures, including attention and vigilance and working memory. In a 2004 survey of 46 neuroscientists and neuropharmacologists conducted in connection with a National Institute of Mental Health schizophrenia initiative, deficits in attention and vigilance and working memory were identified as the most important cognitive deficits in schizophrenia. In other preclinical animal studies conducted under our agreement with Aventis, TC-1827 continued to demonstrate improvement following repeated oral administration without resulting in tolerance and was rapidly absorbed.

In one preclinical study conducted with monkeys, two of ten monkeys given high doses of TC-1827 were found at the end of the study to have low levels of platelets in their blood, a condition known as thrombocytopenia. Because TC-1827 was evaluated in several different preclinical studies involving a total of four different species and thrombocytopenia was seen only in one study with monkeys, we believe that the thrombocytopenia may have been caused by a viral infection in the particular monkeys used in the study. We plan to repeat the study in monkeys in which thrombocytopenia was observed at the same time as we initiate clinical development of TC-1827.

Plans for Future Development. We plan to file an IND and initiate a initial Phase I clinical trial of TC-1827 in the first half of 2005. We also plan to repeat the study of TC-1827 in monkeys described above at the same time as we conduct our initial Phase I trial. If the results of the Phase I trial and the study in monkeys are favorable, we expect to conduct additional Phase I clinical trials and, if the results of those trials are favorable, to conduct a Phase II clinical trial of TC-1827 for the treatment of cognitive impairment associated with schizophrenia.

Pain

We are developing TC-2696 for acute post-operative pain. Depending on clinical trial results, available resources and other considerations, we may pursue development of TC-2696 for other classes of pain as well.

TC-2696

TC-2696 is a novel small molecule that we are developing as an oral treatment for acute post-operative pain. We have completed a Phase I clinical trial of TC-2696. In our preclinical animal studies, TC-2696 demonstrated pain-relieving effects in models of acute, chronic and inflammatory nociceptive pain and of neuropathic pain with comparable or higher potency than morphine or indomethacin, the generally accepted standards of comparison. In these studies, the compound did not result in tolerance following repeated administration, was rapidly absorbed and demonstrated an acceptable toxicology profile.

In our preclinical in vitro studies of TC-2696, we found the compound to be a potent activator of the $\alpha 4\beta 2$ NNR and to avoid interaction with nicotinic acetylcholine receptors in the muscles and ganglia that are associated with side effects. Published studies conducted by third parties have shown that compounds that activate $\alpha 4\beta 2$ have pain-relieving effects in animals. These effects may be caused in part by the activation of NNRs that are abundant in CNS pathways to block the transmission of pain signals to the brain.

Clinical Development of TC-2696

Phase I Clinical Trial. In 2004, we completed a placebo-controlled Phase I single rising dose clinical trial of TC-2696 conducted to determine its safety and tolerability profile in healthy volunteers. The trial was conducted in France with 44 healthy volunteers divided into dose groups of 2mg, 5mg, 10mg, 20mg, 50mg, 100mg, 150mg and 200mg. In the trial, TC-2696 was well tolerated at doses up to 150mg. At 150mg, we observed mild to moderate dizziness and lightheadedness. At 200mg, we observed nausea, vomiting and elevated blood pressure and heart rate.

We included a surrogate measure in our Phase I clinical trial of TC-2696 to provide an indication of the potential efficacy of this product candidate as a treatment for pain. The surrogate measure involved the use of a metal probe, which emitted increasing amounts of heat. We asked participants to indicate when the heat became painful. We then assessed the amount of heat that was necessary at various time intervals following dosing with TC-2696 for participants to feel pain versus the amount of heat that was necessary for participants dosed with placebo to feel pain. Using this measure, we observed a drug effect in participants at one or more intervals in each of the 5mg, 10mg, 50mg and 150mg dose groups.

Plans for Future Development. We plan to initiate a Phase I multiple rising dose clinical trial to further assess the safety and tolerability profile of TC-2696 in the second quarter of 2005. If the results of trial are favorable, we plan to initiate a Phase II clinical trial of TC-2696 in hysterectomy or molar extraction patients in the first half of 2006.

Depression

We are currently conducting a clinical trial of Inversine as an add-on therapy in patients with major depressive disorder. In addition, we have two preclinical product candidates for depression, TC-5214, which is one of the molecular components of Inversine, and TC-2216, which we are developing both for depression and for anxiety disorders.

Inversine and TC-5214

Inversine is currently our only marketed product. Inversine is approved in the United States for the management of moderately severe to severe essential hypertension. We believe that Inversine is prescribed predominantly for the treatment of neuropsychiatric disorders, including Tourette's syndrome, autism and bipolar disorder, in children and adolescents at a lower dose than is used for hypertension. Inversine has been approved for marketing since the 1950s. We acquired marketing rights to the product in August 2002 from Layton Bioscience, Inc., which had previously acquired the rights from Merck & Co., Inc. In connection with our

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acquisition, we assumed Layton's obligations under the agreement pursuant to which Layton acquired the rights from Merck. Pursuant to that agreement, we pay Merck an amount each year based on annual sales of Inversine, subject to a specified annual maximum. Our annual payment obligation to Merck expires in 2008.

Preliminary results of a clinical trial conducted by researchers at Yale University and reported in 2004 showed that mecamylamine hydrochloride, the active ingredient in Inversine, had anti-depressant effects in patients who were not fully responding to fluoxetine hydrochloride, a commonly prescribed anti-depressant marketed as Prozac, when used as an add-on therapy to fluoxetine hydrochloride as compared to when patients were treated with fluoxetine hydrochloride and a placebo. In addition, in a third-party preclinical study published in 2004, rats lacking the β_2 NNR subunit did not respond to a known anti-depressant. We believe that this study suggests a correlation between abnormal β_2 activity and depression. We also believe that Inversine may act to normalize the activity of β_2 . Based in part on these results, we began screening patients for a clinical trial of Inversine as an add-on therapy to citalopram hydrobromide, a commonly prescribed anti-depressant marketed as Celexa, in patients with major depressive disorder in January 2005. We are currently conducting the trial in the United States. We plan to conduct a portion of the trial in India if we receive approval of a regulatory filing comparable to an IND that we have submitted. The trial design provides for enrollment of 150 patients with major depressive disorder who have not responded, or who have only partially responded, to citalopram hydrobromide therapy. The primary efficacy endpoint of the trial is improvement on the Hamilton Rating Scale, an accepted rating scale for depression, as compared to placebo.

TC-5214 is one of the enantiomers of mecamylamine hydrochloride. Enantiomers are chemical substances that are mirror images of each other and have the same chemical but different biological properties. We have licensed from the University of South Florida Research Foundation rights under a pending patent application that, if issued, would provide us with coverage for the composition of TC-5214 for use as a pharmaceutical and for the use of the enantiomer in the treatment of depression and other indications. TC-5214 has shown anti-depressant effects in several preclinical rodent models. If our ongoing Phase II clinical trial of Inversine as an add-on therapy for major depressive disorder is successful, we may accelerate the development of TC-5214 as an add-on therapy for depression.

TC-2216

TC-2216 is a novel small molecule that we are developing as an oral treatment for depression and anxiety disorders. Depression and anxiety disorders often occur together, and anti-depressants are often also used to treat anxiety disorders. In our preclinical studies, TC-2216 showed greater potency than, and anti-depressant effects comparable to, selective serotonin reuptake inhibitors and tricyclics, which are commonly used treatments for depression. In other preclinical studies that we conducted, TC-2216 showed anxiety-relieving effects. In addition, in our preclinical in vitro studies, we found TC-2216 to act on the $\alpha_4\beta_2$ NNR to inhibit the release of neurotransmitters that are involved in mood and to avoid interaction with nicotinic acetylcholine receptors in the muscles and ganglia that are associated with side effects. In 2005, we plan to conduct the additional preclinical toxicology studies necessary to support an IND for clinical trials of TC-2216.

A number of reported studies in humans and animals have linked nicotine to improvements in symptoms of depression. In one of these studies, nicotine administered via patch produced short-term improvements in symptoms in patients with depression based on a significant reduction in scores on the Hamilton Rating Scale after the second day. Because many current anti-depressants do not take effect for two to four weeks, the rapid onset of action of nicotine suggests a potentially significant advantage for drugs that target NNRs to treat depression.

Recent Clinical Developments

In December 2004, we discontinued clinical development of two compounds that were not designed using our Pentad drug discovery technology. We elected to discontinue development of our compound TC-5231, which we had been developing as a treatment for attention deficit hyperactivity disorder, after we determined that, while

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well tolerated in the trial population of children and adolescents between the ages of 6 and 17, it failed to meet defined efficacy endpoints in a Phase II clinical trial. TC-5231 is a low-dose reformulation of mecamylamine hydrochloride, the active ingredient in our product Inversine. Because Inversine has been on the market for many years, we were able to proceed directly to evaluate TC-5231 in a Phase II clinical trial, which reduced our development costs.

We and Dr. Falk Pharma elected to discontinue development of our compound rivanicline, or TC-2403, which we had been developing in collaboration with Dr. Falk Pharma in an enema formulation as a treatment for ulcerative colitis, after we determined that it failed to meet defined efficacy endpoints in a Phase II clinical trial. Pursuant to the terms of a collaboration agreement that we entered into with Dr. Falk Pharma, we shared the development costs of rivanicline evenly with Dr. Falk Pharma.

Our Preclinical Research Programs

We focus our preclinical research efforts on indications for which we believe that selective NNR-targeted drugs have the potential for use in the treatment of disease and for which we believe we can efficiently develop marketable product candidates. In selecting our target indications, we have considered a number of factors, including:

- the availability of preclinical or clinical data that suggest the relevance of NNRs to the indication;
- the size of the potential market opportunity for the indication;
- the projected development time required for a product candidate for the indication to reach the market;
- input received from scientific and medical experts in the indication at meetings that we convene; and
- the existence of well-defined clinical endpoints to assess the efficacy of a product candidate in the treatment of the indication.

Based on our consideration of these factors, we currently have preclinical research programs for schizophrenia, smoking cessation and obesity, in addition to our preclinical product candidates for depression. Each of these indications represents a substantial market opportunity. Our current research objective is to file at least one IND or foreign equivalent each year beginning in 2005.

Schizophrenia

Schizophrenia is a chronic, severe and disabling form of psychosis. Although the precise cause of schizophrenia is unknown, the disease is thought to be associated with an imbalance of neurotransmitter levels in the brain, particularly dopamine levels. Because NNRs act to regulate levels of neurotransmitters in the brain, we believe that NNRs may be useful targets for schizophrenia therapies. A number of published studies have indicated an association between the $\alpha 7$ NNR and schizophrenia. In a 2004 survey of 46 cognitive neuroscientists and neuropharmacologists conducted in connection with a National Institute of Mental Health schizophrenia initiative, $\alpha 7$ was selected more often than any other target as the target of most interest in the development of treatments for psychosis. Because schizophrenic patients are frequently cognitively impaired, we believe that the $\alpha 4\beta 2$ NNR, which plays a role in cognition, also may be associated with schizophrenia. In addition, published studies have linked nicotine to improvements in the ability to filter or disregard unremarkable stimuli, a common symptom of schizophrenia, and cognitive impairment in schizophrenic patients. These studies further suggest the potential relevance of NNRs as targets for the treatment of schizophrenia.

We are evaluating a number of compounds for the treatment of schizophrenia in preclinical studies. Some of these compounds are designed to interact selectively with $\alpha 7$ and others are designed to interact selectively with both $\alpha 7$ and $\alpha 4\beta 2$. In addition, as described above, we are developing our proprietary compound TC-1827, which interacts selectively with $\alpha 4\beta 2$, for the treatment of the cognitive impairment associated with schizophrenia.

Smoking Cessation

Due primarily to nicotine's addictive effects, it is very difficult to quit smoking. Published animal studies have linked nicotine's addictive effects to the release of dopamine in regions in the brain involved in feelings of reward and pleasure. Although the specific NNR implicated in the regulation of dopamine is not fully characterized, several reported studies suggest that the $\beta 2$ NNR may be involved. These studies have shown that selectively blocking $\beta 2$ reduced the rewarding effects of nicotine in mice. Other studies have shown that mice deficient in $\beta 2$ failed to respond to nicotine and had reduced activity in the brain regions associated with reward and pleasure. We are evaluating a number of compounds in a variety of animal models of smoking cessation and nicotine dependence for advancement in our smoking cessation program.

Obesity

A number of published studies have demonstrated that non-smokers generally weigh significantly more than smokers, and nicotine is believed to be responsible. These studies have also shown that smokers gain weight when they stop smoking. Moreover, reported studies with animals have shown that food intake and body weight gain are reduced following repeated administration of nicotine and that the effects are reversed when the nicotine administration is stopped.

As part of our evaluation of our compounds for other indications, we also assess each compound for a preliminary signal of its ability to induce weight loss. We are collecting this data and currently plan to conduct additional preclinical evaluation of the most promising compounds for obesity in 2005.

Our Drug Discovery Technologies—Pentad

We use proprietary databases and computer-based molecular design technologies to identify promising product candidates. We refer to these technologies collectively as Pentad.

We designed Pentad to predict the likelihood that novel compounds will interact with various NNRs, the degree of the interaction and the potential of these compounds to be developed as drugs based on projected pharmacokinetic profiles. Pentad consists of sophisticated computer-based simulation methodologies and extensive biological data from a library of diverse compounds that we have developed and gathered over 20 years. To date, we have applied Pentad specifically in the discovery and optimization of NNR-targeted therapeutics, but we believe it has application to a wide range of targets.

Pentad's virtual screening enables us to more rapidly identify clinically-viable compounds than we believe could be achieved using traditional laboratory synthesis and screening methods. This allows us to reduce drug development time by focusing our resources on compounds that we believe have a greater likelihood of clinical success. We used Pentad to design or optimize ispronidine, TC-1827, TC-2696 and TC-2216.

Our use of Pentad to design new classes of compounds selective for the $\alpha 7$ NNR is another example of its capabilities. We conducted virtual screening of nearly 11,000 compounds and, based on the results, synthesized 115 of them. In preclinical tests, 43 of the synthesized compounds were highly selective to the $\alpha 7$ NNR, showed low binding affinity for NNRs involved in side effects, were bioavailable and passed the blood-brain barrier. We identified the 43 compounds in only six months and are currently evaluating many of these compounds as part of our schizophrenia program.

Strategic Collaborations

We have a collaboration agreement with Aventis Pharma SA that relates to the development and potential commercialization of Aventis compounds. Another collaboration agreement that we entered into with Aventis Pharma for the development of our compounds terminated on January 2, 2005. We also have a development agreement with The Stanley Medical Research Institute. In addition, we have a collaboration agreement with Dr. Falk Pharma GmbH.

Aventis Pharma SA

In January 2002, we entered into a collaborative research, development and commercialization agreement with Aventis. Under the agreement, we granted Aventis a worldwide, sublicensable license under any patent rights that claim methods or materials used for evaluating designated Aventis compounds and our know-how, excluding Pentad, to develop and commercialize those Aventis compounds for Alzheimer's disease and other CNS disorders. Aventis retains worldwide commercialization rights for all compounds that it develops under the agreement.

We could receive up to \$8 million under the agreement upon the achievement of specified pre-commercialization development and regulatory milestones related to Alzheimer's disease and up to \$8 million under the agreement for each other CNS indication upon the achievement of specified pre-commercialization development and regulatory milestones. None of these milestones has been achieved, and the achievement of any of these milestones is uncertain. We are also entitled to receive royalties based on net sales by Aventis, its affiliates and sublicensees of each product under the agreement. Our right to receive royalties would continue on a country-by-country and product-by-product basis until the later of ten years from the first commercial sale of a product in that country or the expiration of the patent rights covering the product in that country. The research term of the agreement expired in December 2004, and Aventis has informed us that it does not intend to extend the research term. We are only eligible to receive milestone payments and royalties from Aventis for any compounds that are selected for further development within six months after the expiration of the research term.

An executive committee comprised of an equal number of representatives from us and Aventis is responsible for initially recommending further development of any compound under the agreement. Aventis also has the independent right to recommend further development of any compound. A scientific review board from Aventis determines whether to advance a compound into clinical development. Under the agreement, Aventis is responsible for conducting all preclinical and clinical development activities and obtaining all required regulatory approvals for compounds selected for advancement. Any compound that Aventis initially selects for advancement but ultimately rejects is terminated from the collaboration and becomes available to us for in-licensing. We would be permitted to in-license the terminated compound for use in indications other than the treatment or prevention of CNS disorders or for use in specified CNS indications if Aventis is not developing its own product for those indications, subject to our making milestone and royalty payments to Aventis.

If not terminated earlier, this agreement terminates upon expiration of all royalty and other payment obligations. In addition, either party may terminate the agreement in the event of an uncured material breach by the other party. However, if Aventis is developing or commercializing more than one compound or product, or if we are developing or commercializing more than one compound or product that has been terminated from the collaboration and in-licensed by us, and the breach relates to a particular compound or product, then the non-breaching party can terminate the agreement only as applied to that compound or product.

In addition, in January 2002, we had also entered into an amended and restated collaborative research and license agreement with Aventis for the development and commercialization of specified Targacept compounds, including ispronicline, for the treatment or prevention of Alzheimer's disease. This agreement terminated on January 2, 2005. As a result, we may pursue the development and commercialization of our product candidates for Alzheimer's disease. While the agreement was in effect, both we and Aventis were restricted from pursuing the development or commercialization of compounds with specified activity at the a4ß2 or a7 NNRs for Alzheimer's disease, except under either the agreement or our other collaboration agreement with Aventis described above. None of our compounds that were subject to this agreement were advanced into clinical development under the agreement.

The Stanley Medical Research Institute

On December 15, 2004, we entered into a development agreement for our compound TC-1827 with The Stanley Medical Research Institute, or SMRI, a nonprofit organization that supports research and development of treatments for schizophrenia. The development term of this agreement is five years and may be extended for

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additional consecutive one-year periods by mutual agreement. During the development term, we are required to use commercially reasonable efforts to conduct a Phase I clinical development program and a Phase II clinical trial of TC-1827 for the treatment of the cognitive impairment associated with schizophrenia in accordance with a development plan that we will prepare.

Upon effectiveness of this agreement, SMRI paid us \$1.25 million in return for our issuance of a convertible promissory note in an equal principal amount. The note bears interest at 10% and matures on January 1, 2007. However, if not earlier paid, the outstanding principal and accrued interest under the note will automatically convert into shares of our common stock concurrently with the completion of this offering at a conversion price equal to the initial public offering price. We could receive up to an additional \$4.25 million from SMRI upon the achievement of specified Phase I and Phase II clinical development milestones for TC-1827. If TC-1827 is successfully developed and commercialized, we will be required to pay to SMRI royalties based on net sales of TC-1827 by us, our affiliates and our licensees. In addition, if intellectual property is generated in the course of the development of TC-1827 that is funded by SMRI and we subsequently sublicense that intellectual property to a third party, we will be required to pay to SMRI a portion of any other amounts that we receive from the sublicensee. Our obligation to continue to make payments to SMRI under the agreement will terminate on various specified future dates if our total payments to SMRI as of any of those dates equal or exceed specified amounts.

We can terminate the agreement if we enter into a development agreement for TC-1827 with a third party that does not relate solely to the manufacturing, sale or promotion of TC-1827. SMRI can terminate the agreement if we abandon the development program or if we propose a change to the development plan for TC-1827 that is rejected by a majority of the members of a development committee. The development committee is comprised of two members that we appoint, one member that SMRI appoints and two other members with experience in the development of schizophrenia therapies that we and SMRI mutually agree upon. In addition, either party may terminate the agreement in the event of an uncured material breach by the other party.

Dr. Falk Pharma GmbH

In January 2001, we entered into a collaborative research, development and license agreement with Dr. Falk Pharma covering the development and commercialization of one of our compounds for the treatment of ulcerative colitis and other gastrointestinal and liver diseases. Upon the effectiveness of this agreement, Dr. Falk Pharma paid us a non-refundable upfront license fee of \$1.0 million and purchased \$1.0 million of our common stock. We and Dr. Falk Pharma have discontinued the development of the lead compound subject to the collaboration agreement after we determined that it failed to meet defined efficacy endpoints in a Phase II clinical trial. There are no compounds in development under this agreement.

Patents and Proprietary Rights

We actively seek to protect the proprietary technology that we consider important to our business, including chemical species, compositions and forms, their methods of use and processes for their manufacture, as well as modified constructs of naturally-expressed receptors, in the United States and other key pharmaceutical markets. We also rely upon trade secrets and contracts to protect our proprietary information.

As of December 31, 2004, our patent estate includes 60 patents issued in the United States, five patent applications allowed in the United States and not yet issued, 20 patent applications pending in the United States, and numerous issued patents and patent applications pending in countries outside the United States. Our issued patents and pending patent applications in the United States include composition of matter coverage on a number of different structural families of compounds. Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. The actual protection afforded by a patent varies from country to country and depends upon many factors, including the type of patent, the scope of its coverage and the availability of legal remedies in a particular country.

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We consider the following United States patents that we own or license to be most important to the protection of our most advanced product candidates.

| <u>Area of Therapeutic Focus</u> | <u>Product Candidate</u> | <u>Patent Scope</u> | <u>Patent Expiration</u> |
|----------------------------------|--------------------------|---|--------------------------------------|
| Cognitive Impairment | Ispronidine (TC-1734) | Composition of matter for a family of compounds that includes TC-1734 | April 2016 |
| | | Methods of use of a family of compounds that includes TC-1734 for treatment and prevention of CNS disorders | February 2017 |
| | | Composition of matter claims to TC-1734 | June 2018—allowed but not yet issued |
| | TC-1827 | Composition of matter for a family of compounds that includes TC-1827 | April 2016 |
| | | Composition of matter claims to TC-1827 | June 2018—allowed but not yet issued |
| | | Method of use of TC-1827 for treatment of CNS disorders, including schizophrenia | June 2018 |
| Pain | TC-2696 | Composition of matter for a family of compounds that includes TC-2696 | April 2016 |
| | | Method of use of a family of compounds that includes TC-2696 for eliciting an analgesic effect | August 2017 |
| Depression | Inversine | Methods of use of mecamylamine for nicotine-responsive psychiatric disorders, including depression | September 2017 |
| | TC-5214 | Methods of use of S-mecamylamine for neuropsychiatric disorders, including depression | December 2019 |

For TC-2216, our product candidate for depression and anxiety disorders, we have a patent application pending in the United States that claims the composition of TC-2216.

In addition to these patents and patent applications, we have later-expiring patents relating to some of these product candidates that cover a particular form or composition, use as part of combination therapy or method of preparation or use. These patents could provide additional or a longer period of protection. We also have patent applications pending that seek equivalent or substantially comparable protection for our product candidates in key international markets.

License Agreements

We are parties to five license agreements that are important to our business.

University of South Florida Research Foundation

Pursuant to a license agreement with the University of South Florida Research Foundation, or USFRF, we hold an exclusive worldwide license to patents and patent applications owned by USFRF for use in the development and commercialization of mecamylamine hydrochloride and other specified compounds. The licensed patents and patent applications include an issued patent covering methods of use for the treatment of

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depression, attention deficit hyperactivity disorder, Tourette's syndrome and nicotine-responsive neuropsychiatric disorders and pending patent applications covering the pharmaceutical composition of the molecular components of mecamylamine hydrochloride. Under the agreement, we are obligated to pay to USFRF:

- an annual license fee until a new drug application or its equivalent is filed to cover the use of a product subject to the license to treat a neuropsychiatric disorder;
- an annual fee to maintain our rights of first refusal to acquire rights to the licensed patents and patent applications beyond the scope of our current license;
- royalties on net sales of products subject to the license or a percentage of royalties received from a sublicensee;
- aggregate payments of up to \$200,000 based on the achievement of specified regulatory milestones; and
- a percentage of other amounts that we receive from a sublicensee.

The aggregate annual license fees are creditable, up to a specified amount per year, against future royalties.

We are required to use commercially reasonable efforts to develop or to market and sell a product covered by the agreement. In particular, we are required to spend a specified minimum amount on research and development of products covered by the agreement each year until we receive marketing approval for a covered product. If USFRF believes that we are not meeting our diligence obligation, it is entitled to terminate the agreement following a cure period. If we do not agree with USFRF's determination, we can submit the matter to binding arbitration. In addition, if we have not received marketing approval of a product covered by the agreement on or before December 31, 2012, USFRF can make our license nonexclusive.

We may terminate the agreement at any time. If not earlier terminated, the agreement will terminate upon expiration of the last to expire of the licensed patent rights.

Virginia Commonwealth University Intellectual Property Foundation

Pursuant to a license agreement with Virginia Commonwealth University Intellectual Property Foundation, or VCUIPF, we hold a non-exclusive worldwide license to patents covering a method of use of a family of compounds that includes TC-2696 for eliciting an analgesic effect. Under the agreement, we are obligated to pay to VCUIPF:

- an annual license fee and an additional annual fee to maintain the right at any time to convert the license into an exclusive license for an additional fee;
- royalties on net sales of products subject to the license or a percentage of amounts received from a sublicensee; and
- aggregate payments of up to \$900,000 based on the achievement of specified development and regulatory milestones.

We are required to use reasonable efforts to bring one or more products covered by the agreement to market. We may terminate the agreement at any time with 90 days notice. If the agreement is not earlier terminated, our obligation to pay royalties under the agreement will terminate upon expiration of the licensed patent rights.

Wake Forest University Health Sciences

Pursuant to a license agreement with Wake Forest University Health Sciences, or WFUHS, we hold an exclusive worldwide license to patents covering a method of use of a family of compounds that includes TC- 2696 for the treatment of chronic or female-specific pain. Under the agreement, we paid WFUHS a non-refundable upfront license fee of \$25,000 and are obligated to pay to WFUHS:

- royalties on net sales of products subject to the license or, if less, a percentage of amounts received from a sublicensee;

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- aggregate payments of up to \$878,000 per product subject to the license based on the achievement of specified development and regulatory milestones; and
- a percentage of other amounts that we receive from a sublicensee.

We are required to use commercially reasonable efforts to pursue the development of at least one product covered by the agreement and to bring at least one such product to market. We may terminate the agreement at any time with 60 days notice. If not earlier terminated, the agreement will terminate upon expiration of the last to expire of the licensed patent rights.

University of Kentucky Research Foundation

Pursuant to a sponsored research agreement, the University of Kentucky Research Foundation, or UKRF, agreed to assign to R.J. Reynolds Tobacco Company UKRF's rights to inventions that resulted in patents related to ispronicline, TC-1827, TC-2696 and other earlier-stage compounds in our portfolio. These patents were subsequently assigned by RJR to us in August 2000. Under the sponsored research agreement and a subsequent license agreement with UKRF, we are obligated to pay royalties to UKRF with respect to products covered by these patents. In addition, under the license agreement, RJR paid UKRF an upfront license fee of \$20,000.

Medical College of Georgia Research Institute

Pursuant to a license agreement with Medical College of Georgia Research Institute, or MCGRI, we hold an exclusive worldwide license to a patent covering a method of use of a substance that stimulates the activity of nicotinic acetylcholine receptors by inhibiting the activity of another class of receptors, a method of use of increasing the presence of a therapeutic substance to treat neurodegeneration and a screening method. Under the agreement, we paid MCGRI an upfront license fee of \$25,000 and are obligated to pay to MCGRI:

- royalties on net sales of products subject to the license, with an annual minimum of \$12,000 beginning in the first year of product sales;
- aggregate payments of up to \$425,000 based on the achievement of specified development and regulatory milestones; and
- a percentage of other amounts that we receive from a sublicensee.

If not earlier terminated, the agreement will terminate upon the earlier of expiration of the licensed patent rights or July 2027.

Trade Secrets

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. For example, we maintain Pentad as an unpatented trade secret. We seek to protect our proprietary information, in part, using confidentiality agreements with our commercial partners, collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention assignment agreements with some of our commercial partners and consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Sales and Marketing

We currently have limited sales and distribution capabilities and limited experience in marketing and selling pharmaceutical products. Our current strategy is to selectively enter into collaboration agreements with third parties for target indications in which our potential collaborator has particular expertise or that involve a large, primary care market that must be served by large sales and marketing organizations. In entering into these collaboration agreements, our goal will be to maintain co-promotion or co-commercialization rights in the United States and, in some cases, other markets. In order to implement our strategy successfully, we must develop a specialized sales and marketing organization with sufficient technical expertise. Our product currently available in the market, Inversine, is distributed by a third party pursuant to an exclusive distribution agreement.

Manufacturing

All of our product candidates are compounds of low molecular weight, commonly referred to as small molecules. We have selected these compounds in part for their ease of synthesis and the low cost of their starting materials. All of our current product candidates are manufactured in a simple synthetic process from readily available starting materials. We expect to continue to develop drug candidates that can be produced cost-effectively by third-party contract manufacturers.

We are able to manufacture the quantities of our product candidates necessary for relatively short preclinical toxicology studies ourselves. We believe that this allows us to accelerate the drug development process by not having to rely on a third party for all of our manufacturing needs. However, we do rely and expect to continue to rely on a number of contract manufacturers to produce enough of our product candidates for use in more lengthy preclinical research. We also depend on these contract manufacturers to manufacture our product candidates in accordance with current good manufacturing practices, or cGMP, for use in clinical trials. We will ultimately depend on contract manufacturers for the manufacture of our products for commercial sale, as well as for process development. Contract manufacturers are subject to extensive governmental regulation.

Third parties currently manufacture Inversine and its active ingredient for us. Also, we have entered into a development and production agreement with Siegfried Ltd. Under this agreement, Siegfried has agreed to provide us with process development services and clinical trial material at specified rates for product candidates that we elect to introduce into the agreement. We have also agreed, following marketing approval or anticipated marketing approval of any product candidate for which Siegfried performs services under the agreement, to negotiate for a separate multi-year commercial supply agreement with Siegfried for a substantial percentage of our contracted supply needs for that product candidate, except in limited circumstances. Beginning in February 2006, either we or Siegfried can terminate the agreement at any time on 12 months notice or immediately in the event of an uncured material breach by the other party.

Competition

Our industry is subject to rapid and intense technological change. We face, and will continue to face, worldwide competition from biotechnology, biopharmaceutical and pharmaceutical companies, research institutions, government agencies and academic institutions. Many of these competitors are established in the CNS field and are developing and commercializing pharmaceutical products that would compete with our product candidates that are approved for marketing. Many of our competitors and potential competitors have more resources than we do and have already successfully developed and marketed drugs. Mergers and acquisitions in the pharmaceutical industry may result in even greater resources being concentrated in our competitors.

We also face substantial competition from therapies designed to target NNRs. We are aware of several prominent pharmaceutical companies with product candidates designed to target NNRs in development, including Pfizer, with an NNR-targeted compound in Phase III for smoking cessation, and Abbott Laboratories, with an NNR-targeted compound in Phase II for Alzheimer's disease, ADHD and schizophrenia and a second NNR-targeted compound in Phase I for pain. In addition, we believe that other companies have active NNR-based research programs, including, Merck & Co., AstraZeneca, Eli Lilly, Sanofi-Synthelabo, Memory Pharmaceuticals, Critical

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Therapeutics and NeuroSearch A/S. We expect to face increased competition in the future if NNR-targeted therapeutics are further validated and if companies initiate or grow NNR-based programs or otherwise enter the CNS market.

In addition, there are several pharmaceutical companies in the United States and globally that currently market and sell drugs for indications that we are targeting. There is currently no approved product either for AAMI or for cognitive impairment associated with schizophrenia. We believe that the primary competitive products for use in the other indications that we are currently targeting include:

- for mild to moderate Alzheimer's disease, acetylcholinesterase inhibitors such as Aricept from Pfizer, Reminyl from Johnson & Johnson and Exelon from Novartis and for moderate to severe Alzheimer's disease, Namenda from Forest Laboratories, which acts by regulating the neurotransmitter glutamate;
- for pain, non-steroidal anti-inflammatory drugs such as Celebrex from Pfizer and opioids such as OxyContin from Purdue Pharma;
- for depression, selective serotonin reuptake inhibitors such as Prozac from Eli Lilly, Paxil/Seroxar from GlaxoSmithKline, Zoloft from Pfizer, Celexa from Forest Laboratories and Lexapro from Forest Laboratories and the dual uptake inhibitor Effexor from Wyeth;
- for schizophrenia, anti-psychotics such as Zyprexa from Eli Lilly, Risperdal from Johnson & Johnson and Abilify from Bristol-Myers Squibb; and
- for smoking cessation, Zyban from GlaxoSmithKline.

Many of these products have well-known brand names, are distributed by large pharmaceutical companies with substantial resources and have achieved widespread acceptance among physicians and patients. Furthermore, pharmaceutical and biotechnology companies are currently developing additional treatments for the indications that we are targeting that may be approved for marketing and sale prior to any approval of our product candidates.

We expect to compete based upon, among other things, the efficacy of our products and favorable side effect profiles. Our ability to compete successfully will depend on our continued ability to attract and retain skilled and experienced scientific, clinical development and executive personnel, to identify and develop viable product candidates and to exploit these products and compounds commercially before others are able to develop competitive products. In addition, our ability to compete may be affected by insurers and other third-party payors encouraging the use of generic products. This may have the effect of making branded products less attractive from a cost perspective to buyers.

Government Regulation

Drug Regulation in the United States

The research, testing, manufacture and marketing of drug products are extensively regulated by the FDA and other governmental authorities in the United States. The Federal Food, Drug and Cosmetic Act and other federal and state statutes and regulations regulate the research, development, testing, manufacture, storage, record keeping, labeling, promotion and marketing and distribution of drug products.

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

- preclinical laboratory tests, preclinical studies in animals and formulation studies;
- the submission of an IND to the FDA, or comparable documents to regulatory bodies in foreign countries in which clinical trials are to be held, which must become effective before clinical trials may begin;
- adequate and well-controlled clinical trials to establish the safety and efficacy in humans of the drug for each indication;
- the submission of a new drug application, or NDA, to the FDA using the Common Technical Document, a format for non-clinical, clinical and quality data acceptable to regulatory authorities in the United States, European Union and Japan; and

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- FDA review and approval of the NDA before any commercial sale or shipment of the drug.

Preclinical tests typically include laboratory evaluation of product chemistry, formulation and stability, as well as animal studies to evaluate toxicity and metabolism. The results of preclinical tests are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of an IND before clinical testing in humans may begin. If the FDA has not advised otherwise within this 30-day period, the proposed trial may begin. If the FDA has comments or questions, they must be resolved to the satisfaction of the FDA before the trial can begin. In addition, the FDA may halt proposed or ongoing clinical trials at any time, in which event the trial cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA. The IND application process may be extremely costly and substantially delay development of product candidates. Moreover, positive results in preclinical tests do not ensure positive results in clinical trials.

Clinical trials involve the administration of the drug to healthy volunteers or patients under the supervision of a qualified principal investigator. Clinical trials must be conducted in compliance with federal regulations and requirements and under established protocols. These protocols detail the objectives of the clinical trial, the parameters to be used in monitoring safety and the efficacy criteria to be evaluated. The study protocol and informed consent information for patients in clinical trials must also be approved by an institutional review board at each institution where the clinical trials are conducted.

Clinical evaluation involves a time-consuming and costly process, typically involving the following three phases:

- Phase I clinical trials are conducted with a small number of healthy human volunteers as subjects to determine an early safety and tolerability profile, including side effects associated with increasing doses, a maximum tolerated dose and pharmacokinetics;
- Phase II clinical trials are conducted with groups of patients afflicted with the therapeutic condition for which the investigational drug is being tested with a specific disease in order to determine potential efficacy preliminarily, and an expanded safety profile that identifies possible adverse effects; and
- Phase III clinical trials are large-scale, geographically diverse, adequate and well-controlled, conducted with patients afflicted with a target disease in order to collect data to establish the safety and efficacy profile and assure compliance with the requirements of the Federal Food, Drug and Cosmetic Act.

The FDA, the study sponsor and the institutional review boards reviewing each clinical trial site closely monitor the progress of each of the three phases of clinical trials that are conducted in the United States. They may change or terminate the testing based upon the data accumulated to that point and their assessment of the relative risks and benefits to the patient.

Upon successful completion of Phase III trials, a company may submit an NDA including the results of preclinical studies and clinical trials and data relating to the product candidate's chemistry, pharmacology, manufacture, safety and effectiveness to the FDA in order to obtain approval to market the product in the United States. This submission is expensive, both in terms of studies required to generate and compile the requisite data and the significant user fees required for NDA submission.

The FDA has 45 days from its receipt of an NDA to determine if it will accept the filing for a substantive review. The FDA may refuse the filing, which would result in the loss of 50% of the application user fee. If the FDA accepts the filing, it begins an in-depth review. Under current performance goals, the FDA has either 180 or 365 days to respond, depending upon whether the review is classified by the FDA as priority or standard. The FDA often extends the review timeline by requesting additional information or clarification. The FDA may refer issues to an advisory committee for review, evaluation and recommendation as to whether the application should be approved, but the FDA is not bound by any recommendation of an advisory committee.

If the FDA's evaluation of the NDA and the manufacturing facilities are favorable, the FDA may issue an approval letter, or, in many cases, an approvable letter followed by an approval letter. An approvable letter usually contains a number of conditions that must be met in order to secure final approval. If the FDA decides

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that the conditions have been met, it will issue an approval letter. An approval letter makes a drug available for physicians to prescribe in the United States, but authorizes commercial marketing of the drug only for specific indications. After a drug has been approved for a particular indication, other trials and studies may be conducted to explore its use for treatment of new indications.

The FDA may also refuse to approve an NDA, or may issue a not approvable letter. A not approvable letter outlines the deficiencies in the submission and often requires additional testing or information. Even if the applicant completes the additional testing and submits additional information, the FDA may ultimately decide that the application does not satisfy the regulatory criteria for approval.

Satisfaction of FDA pre-market approval requirements for new drugs typically takes several years. The actual time required may vary substantially based upon the type, complexity and novelty of the product or target disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and require costly procedures. Success in early stage clinical trials does not assure success in later stage clinical trials. Data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations that could delay, limit or prevent regulatory approval.

Even if a drug receives regulatory approval, the FDA may require post-marketing studies, sometimes referred to as Phase IV studies, to monitor the effects of approved drugs and may limit further marketing based on the results of these post-marketing studies. Moreover, the FDA may impose restrictions on the drug or withdraw its approval if a company does not stay in compliance with pre- and post-market regulatory standards or if problems relating to safety or effectiveness of the drug occur after it reaches the marketplace. The FDA has broad post-market regulatory and enforcement powers, including the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products and withdraw approvals.

Once an NDA is approved, the product it covers becomes a listed drug that 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 is therapeutically equivalent to a marketed drug. This means, among other things, that it has the same active ingredients in the same strengths and dosage form as the listed drug, and has been demonstrated to be bioequivalent to the listed drug. There is generally no requirement, other than the requirement for evidence of bioequivalence, for an ANDA applicant to conduct or submit results of preclinical tests or clinical trials to establish the safety or efficacy of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA and can generally 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 drug that contains previously approved active ingredients but is approved in a new dosage, dosage form or route of administration, or for a new use if new clinical trials were required to support the approval. During this three-year exclusivity period, the FDA cannot grant approval of an ANDA for a generic version of the listed drug. However, the FDA can approve generic equivalents of that listed drug based on other listed drugs with the same active ingredient, such as a generic that is the same in every way but its indication for use, and thus the value of this exclusivity may be limited. Federal law also provides a period of five years of exclusivity following approval of a drug that does not contain any previously approved active ingredients. During the five-year exclusivity period, no ANDA for a generic version of the listed drug can be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval.

In addition, applicants submitting an ANDA for a drug that has listed patents are required to make one of four certifications regarding each listed patent, which may include certifying that one or more listed patents are invalid or not infringed. If an applicant certifies invalidity or non-infringement, it is required to provide notice of its filing to the new drug application sponsor and the patent holder. If the patent holder then initiates a suit for patent infringement against the ANDA applicant within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA until either 30 months has passed or there has been a court decision holding that the patents in question are invalid or not infringed. The first of the ANDA applicants submitting substantially complete applications certifying that listed patents for a particular product are invalid or not infringed may

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qualify for an exclusivity period of 180 days, which runs from the date the generic product is first marketed. Until any effective 180-day exclusivity expires, the FDA cannot grant effective approval of subsequently submitted ANDAs.

The manufacturers of approved drugs and their manufacturing facilities are subject to continuous review and periodic inspections by the FDA and must comply with the FDA's current good manufacturing process, or cGMP, regulations. A manufacturer will be subject to possible legal or regulatory action, such as suspension of manufacturing, seizure of product or recall of a product, if it does not comply with the FDA's rules. We intend to contract with third parties to manufacture our products, and our ability to control their compliance with FDA requirements will be limited.

We must also notify the FDA of any change in an approved product beyond variations already allowed in the approval. Changes to the product, its labeling or its manufacturing could require prior FDA approval and may require further clinical investigations to support the change. Such approvals may be expensive and time-consuming, and if not approved, the product will not be allowed to be marketed as modified.

The FDA also imposes a number of complex regulations on entities that advertise and promote marketed pharmaceuticals. These regulations include requirements for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. The FDA enforces the regulations under the Federal Food Drug and Cosmetic Act. Failure to abide by these regulations can result in penalties, including the issuance of a warning letter mandating the correction of deviations from FDA standards or the publication of corrective advertising. They may also include a requirement that future advertising and promotional materials be pre-cleared by the FDA, as well as civil and criminal investigations and prosecutions.

Holders of an NDA are also subject to laws and regulations regarding non-clinical laboratory practices that support human safety and product distribution, the experimental use of animals and the use and disposal of hazardous or potentially hazardous substances. In each of these areas, the FDA has broad regulatory and enforcement powers, including the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals.

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

Fast Track Designation

Congress enacted the Food and Drug Administration Modernization Act of 1997, or FDAMA, in part, to ensure the timely availability of safe and effective drugs, biologics and medical devices by expediting the FDA review process for some new products. FDAMA establishes a statutory program for the approval of a so-called fast track product, defined as a new drug or biologic intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for that condition. Under the fast track program, the sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a fast track product at any time during clinical development of the product. Fast track designation provides for an expedited review of a product, which is intended to accelerate FDA approval. Although we have not yet requested fast track designation for any of our product candidates, we may seek fast track designation in the future. We will never be sure that we will obtain fast track designation. We cannot predict the ultimate impact, if any, of the fast track process on the timing or likelihood of FDA approval of any of our potential products.

Drug Regulation Outside the United States

In addition to U.S. regulations, we are subject to a variety of foreign regulations governing clinical trials and potential commercial sales and distribution of our products and product candidates. Even if we obtain FDA approval for a product, we must obtain approval of a product by the regulatory authorities of foreign countries

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before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Under European Union regulatory systems, we may submit marketing authorizations either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this latter procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessment report, each member state must decide whether to recognize approval.

Third-Party Reimbursement

In the United States, European Union and elsewhere, sales of pharmaceutical products depend in part on the availability of reimbursement to the patient from third-party payors, such as government health administrative authorities, managed care providers and private insurance plans. Third-party payors are increasingly challenging the prices charged for medical products and services and examining their cost-effectiveness. For example, the European Union generally provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement. It is possible that none of our product candidates that receive marketing approval will be considered cost-effective or that reimbursement to patients will not be sufficient to allow us to maintain price levels that enable us to realize a satisfactory return on our investment in product development.

Price Controls

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 governmental pricing control on pharmaceutical products. In some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union generally provides options for its member states to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. We do not know whether any country that has price controls will allow favorable pricing arrangements for any of our product candidates.

Employees

As of December 31, 2004, we had 73 full-time employees, 30 of whom are Ph.D.s, M.D.s or both. Our management believes that relations with our employees are good. None of our employees is represented under a collective bargaining agreement.

Property and Facilities

We lease approximately 40,000 square feet of laboratory and office space located in the Piedmont Triad Research Park in Winston-Salem, North Carolina. We have rights exercisable until March 31, 2006 to lease additional space in this facility. The term of our lease expires August 1, 2007, and we have a renewal option for an additional five-year term. If we elect to renew the lease, we will have rights to lease additional space in this facility during the renewal term. The current monthly payment under our lease is approximately \$123,000. We believe that our leased facilities, together with our rights to lease additional space, are adequate to satisfy our current needs.

Legal Proceedings

We are not currently a party to any material legal proceedings.

MANAGEMENT

Executive Officers and Directors

The name, age and position of our executive officers and directors as of December 31, 2004 are as follows:

| <u>Name</u> | <u>Age</u> | <u>Position</u> |
|---------------------------------|------------|--|
| Mark Skaletsky (1) (2) | 56 | Chairman of the Board of Directors |
| J. Donald deBethizy, Ph.D. | 54 | Chief Executive Officer, President and Director |
| Merouane Bencherif, M.D., Ph.D. | 50 | Vice President, Preclinical Research |
| Jeffrey P. Brennan | 47 | Vice President, Business and Commercial Development |
| William S. Caldwell, Ph.D. | 51 | Vice President, Drug Discovery and Development |
| Geoffrey C. Dunbar, M.D. | 57 | Vice President, Clinical Development and Regulatory Affairs |
| Alan A. Musso | 43 | Vice President, Chief Financial Officer, Treasurer and Secretary |
| M. James Barrett, Ph.D. (1) | 62 | Director |
| Charles A. Blixt (2) (3) | 53 | Director |
| G. Steven Burrill (3) | 60 | Director |
| Errol B. De Souza, Ph.D. (2) | 51 | Director |
| Elaine V. Jones, Ph.D. (1) (2) | 50 | Director |
| John P. Richard (3) | 47 | Director |
| Alan G. Walton, Ph.D. | 68 | Director |

- (1) Member of the Compensation Committee.
- (2) Member of the Governance and Nominating Committee.
- (3) Member of the Audit Committee.

Mark Skaletsky has been a member of our board of directors since February 2001 and has been our Chairman since January 2002. Since March 2001, he has been the chairman and chief executive officer of Trine Pharmaceuticals, Inc., formerly Essential Therapeutics, Inc., a privately held drug discovery and development company. From May 1993 to January 2001, Mr. Skaletsky was the president and chief executive officer of GelTex Pharmaceuticals, Inc., a publicly traded pharmaceutical company. Mr. Skaletsky is a member of the boards of directors of Paradigm Genetics, Inc., Isis Pharmaceuticals, Inc., ImmunoGen, Inc. and Advanced Magnetics, Inc., each of which is a publicly traded company. Essential Therapeutics and its wholly owned subsidiaries filed for protection under Chapter 11 of the United States Bankruptcy Code in May 2003. The plan of reorganization for Essential Therapeutics became effective in October 2003 by order of the United States Bankruptcy Court for the District of Delaware, and Essential Therapeutics was renamed Trine Pharmaceuticals, Inc. in November 2003.

J. Donald deBethizy, Ph.D. has been our Chief Executive Officer and a member of our board of directors since August 2000. Dr. deBethizy has been our President since March 1997. From March 1985 to March 1997, Dr. deBethizy worked for R.J. Reynolds Tobacco Company in various capacities, most recently as vice president of product evaluation, research and development. Dr. deBethizy has been an adjunct professor in the Department of Physiology and Pharmacology at Wake Forest University School of Medicine since October 1991 and has been an adjunct professor of toxicology in the Integrated Toxicology Program at Duke University since May 1988.

Merouane Bencherif, M.D., Ph.D. has been our Vice President, Preclinical Research since August 2002. He was our Vice President, Biological Sciences from August 2000 to August 2002 and our Senior Manager and Director of Pharmacology and Clinical Sciences from February 1999 to August 2000. From July 1993 to February 1999, Dr. Bencherif worked for R.J. Reynolds Tobacco Company's Research and Development (Pharmacology) Department in various capacities as a scientist, most recently as a master scientist from March 1998 to February 1999. Dr. Bencherif was an adjunct assistant professor from March 1996 to March 2002 and, since March 2002, has been an associate professor in the Department of Physiology and Pharmacology at Wake Forest University School of Medicine.

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Jeffrey P. Brennan has been our Vice President, Business and Commercial Development since September 2003. From September 2000 to May 2003, Mr. Brennan was vice president, commercial development at Sanofi-Synthélabo Inc., a publicly traded global pharmaceutical company based in Paris, France. From November 1996 to September 2000, Mr. Brennan served as vice president, business development at Sanofi-Synthélabo.

William S. Caldwell, Ph.D. has been our Vice President, Drug Discovery and Development since August 2000. From January 1999 to August 2000, Dr. Caldwell was our Director, Chemistry and Operations.

Geoffrey C. Dunbar, M.D. has been our Vice President, Clinical Development and Regulatory Affairs since June 2001. From January 1997 to June 2001, Dr. Dunbar was vice president, clinical development – neurosciences at Bristol-Myers Squibb Company, a publicly traded global pharmaceutical company.

Alan A. Musso has been our Vice President, Chief Financial Officer, Treasurer and Secretary since February 2002. From February 2001 to February 2002, Mr. Musso was vice president and chief financial officer of Osiris Therapeutics, Inc., a privately held biotechnology company. From April 1997 to February 2001, Mr. Musso was the chief financial officer for Cato Research & Cato Holding Company, a privately held global contract research organization. Mr. Musso also was the chief financial officer of Vascular Genetics, Inc., a privately held gene therapy company, from October 1997 to February 2000. In addition, Mr. Musso was employed by Pfizer Inc., a publicly traded global pharmaceutical company, from April 1989 to December 1994, first as a senior auditor and then as a general accounting manager for one of Pfizer's manufacturing facilities. Mr. Musso is a certified public accountant and a certified management accountant.

M. James Barrett, Ph.D. has been a member of our board of directors since December 2002. Since September 2001, Dr. Barrett has been a general partner of New Enterprise Associates, a venture capital firm that focuses on the medical and life sciences and information technology industries. From 1997 to 2001, he was chairman and chief executive officer of Sensors for Medicine and Science, Inc., a privately held company that he founded and which develops optical chemical sensing technologies. He continues to serve as its chairman and is a member of the boards of directors of the publicly traded companies MedImmune, Inc. and Pharmion Corporation.

Charles A. Blixt has been a member of our board of directors since August 2000. Since January 1998, he has been executive vice president and general counsel of R.J. Reynolds Tobacco Company. Since June 1999, he has been executive vice president, general counsel and assistant secretary of R.J. Reynolds Tobacco Holdings, Inc., the parent company of R.J. Reynolds Tobacco Company.

G. Steven Burrill has been a member of our board of directors since August 2000. Since January 1994, he has been chief executive officer of Burrill & Company LLC, a merchant bank that he founded. Prior to founding Burrill & Company LLC, Mr. Burrill spent 27 years with Ernst & Young LLP, including the last 17 as a partner of the firm. He is chairman of the board of Paradigm Genetics, Inc. and a member of the boards of directors of DepoMed, Inc. and Third Wave Technologies, Inc., each of which is a publicly traded company.

Errol B. De Souza, Ph.D. has been a member of our board of directors since January 2004. Since March 2003, he has been president, chief executive officer and a director of Archemix Corporation, a privately held biotechnology company. From September 2002 to March 2003, he was president, chief executive officer and a director of Synaptic Pharmaceutical Corporation, a publicly traded biopharmaceutical company that was acquired by H. Lundbeck A/S in March 2003. From December 1999 to September 2002, he was senior vice president and site head of U.S. drug innovation & approval (research and development) of Aventis Pharma SA, a pharmaceutical company formed by the merger of Hoechst Marion Roussel and Rhone-Poulenc Rorer Inc. From September 1998 until December 1999, Dr. De Souza was senior vice president and global head, lead generation of Hoechst Marion Roussel. In 1992, Dr. De Souza co-founded Neurocrine Biosciences, Inc., a publicly traded biopharmaceutical company. Dr. De Souza is a member of the boards of directors of IDEXX Laboratories, Inc. and Palatin Technologies, Inc., each of which is a publicly traded company.

Elaine V. Jones, Ph.D. has been a member of our board of directors since August 2000. Since August 2003, she has been a general partner of EuclidSR Associates, L.P., which is the general partner of EuclidSR

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Partners, L.P., a venture capital fund that focuses on life sciences and information technology companies. Dr. Jones was an investment manager from June 1999 to September 2001, and was a vice president from September 2001 to August 2003, for S.R. One, Limited, a venture capital subsidiary of SmithKline Beecham.

John P. Richard has been a member of our board of directors since November 2002. Since April 1999, he has been an independent biotechnology consultant. He also has been a business advisor to GPC Biotech AG, a drug discovery and development company based in Munich, Germany and traded on the Frankfurt Stock Exchange, since April 1999. Prior to April 1999, Mr. Richard served as executive vice president, business development of SEQUUS Pharmaceuticals, Inc., a publicly traded biotechnology company that became a wholly owned subsidiary of ALZA Corporation in March 1999.

Alan G. Walton, Ph.D. has been a member of our board of directors since March 2003. He joined Oxford Partners, a venture capital firm, as a general partner in March 1987. In July 1992, Dr. Walton founded Oxford Bioscience Partners, a life science venture capital firm where he is a general partner. He is chairman of the board of directors of the management company Oxford Bioscience IV Corporation and serves as a member of the board of directors of Alexandria Real Estate Equities, Inc. and ACADIA Pharmaceuticals Inc., both of which are publicly traded companies. Dr. Walton is also a founder of Human Genome Sciences, Inc. and Gene Logic Inc., both of which are publicly traded companies.

Board Composition

Our board of directors consists of nine members, each of whom was elected in accordance with the terms of a stockholders agreement that will terminate upon the completion of this offering. With the exception of Dr. deBethizy, all of our directors are “independent directors” within the meaning of NASDAQ regulations. There are no family relationships among any of our directors or executive officers.

Following the completion of this offering, our board of directors will consist of nine members divided into three classes:

- Class I, for a term expiring at the 2005 annual meeting of stockholders;
- Class II, for a term expiring at the 2006 annual meeting of stockholders; and
- Class III, for a term expiring at the 2007 annual meeting of stockholders.

At each annual meeting of stockholders after the initial classification, or at a special meeting in lieu of an annual meeting, a class of directors will be elected to serve for a three-year term to succeed the directors of the same class whose terms are then expiring. Our Class I directors will be Elaine V. Jones, John P. Richard and Alan G. Walton. Our Class II directors will be M. James Barrett, Charles A. Blixt and J. Donald deBethizy. Our Class III directors will be G. Steven Burrill, Errol B. De Souza and Mark Skaletsky.

Board Committees

Audit Committee. The members of our audit committee are Messrs. Burrill, Blixt and Richard. Mr. Burrill chairs the committee. The audit committee assists the board of directors in its oversight of our accounting, financial reporting and internal control functions. Specific responsibilities of our audit committee include:

- oversight of the audits of our financial statements and our internal control over financial reporting;
- monitoring the performance of our independent auditors, including determining whether to engage or dismiss the independent auditors and to assess the independent auditors’ qualifications and independence;
- oversight of our compliance with legal and regulatory requirements, including approval of related party transactions and establishment of procedures for the receipt, retention and treatment of complaints regarding accounting, internal accounting controls and auditing matters; and
- preparing the report required to be included in our annual proxy statement in accordance with Securities and Exchange Commission rules and regulations.

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Compensation Committee. The members of our compensation committee are Mr. Skaletsky, Dr. Barrett and Dr. Jones. Mr. Skaletsky chairs the committee. The purpose of our compensation committee is to discharge the responsibilities of our board of directors relating to compensation of our executive officers. Specific responsibilities of our compensation committee include:

- establishing and periodically reviewing our compensation philosophy and the adequacy of compensation plans and programs for our executive officers and other employees;
- establishing compensation arrangements and incentive goals for our executive officers and administering compensation plans;
- reviewing the performance of our executive officers and awarding incentive compensation and adjusting compensation arrangements as appropriate based upon performance; and
- preparing our report on executive compensation for inclusion in our annual proxy statement in accordance with Securities and Exchange Commission rules and regulations.

Governance and Nominating Committee. The members of our governance and nominating committee are Messrs. Skaletsky and Blixt and Drs. De Souza and Jones. Mr. Skaletsky chairs the committee. Specific responsibilities of our governance and nominating committee include:

- identifying individuals qualified to serve as directors, recommending to our board of directors nominees for election at our annual meetings of stockholders and recommending to our board of directors individuals to fill vacancies on the board;
- making recommendations to the board of directors concerning the criteria for board membership and the size, composition and compensation of the board of directors and its committees;
- assisting the board of directors in establishing and maintaining effective corporate governance practices and procedures; and
- conducting an annual review of the effectiveness of the board of directors and its committees.

Compensation Committee Interlocks and Insider Participation

None of our executive officers serves as a member of the board of directors or compensation committee, or other committee serving an equivalent function, of any other entity that has one or more of its executive officers serving as a member of our board of directors or our compensation committee. None of the members of our compensation committee has ever been our employee.

Director Compensation

In the past, each of our directors who is not our employee has received a nonqualified stock option to purchase 25,000 shares of our common stock upon his or her initial election to our board of directors. Additionally, upon each non-employee director's annual reelection, he or she has been granted a nonqualified stock option to purchase 7,500 shares of common stock. However, our chairman received a nonqualified stock option to purchase 35,000 shares upon his or her initial election and a nonqualified stock option to purchase 12,500 shares upon his or her annual reelection. Each of these options:

- has a ten-year term;
- has an exercise price of \$0.01 per share; and
- vests one year after the date of grant if the director attended at least 75% of the regular board meetings held during that year.

In lieu of any such nonqualified stock option, each non-employee director could elect to receive a restricted stock award for the same number of shares of stock at a purchase price of \$0.01 per share. Each non-employee director that is not a designee of one of our investors or a group of our investors has received, in addition to the equity compensation described above, cash compensation in the amount of \$10,000 per year as an annual

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retainer. Each director is reimbursed for expenses incurred in connection with his or her attendance at meetings of the board of directors and its committees. We have not historically paid any additional compensation for service on any committees of the board of directors.

We have adopted a new director compensation program that will become effective concurrently with the completion of this offering. Each non-employee director will receive an annual cash retainer of \$20,000 payable in quarterly installments. Each member of a committee of the board will receive an additional annual cash retainer of \$2,500, the chairman of our audit committee will receive an additional annual cash retainer of \$7,500 and the chairman of each of our compensation and governance and nominating committees will each receive an additional annual cash retainer of \$2,500. Each non-employee director also will receive an option for 25,000 shares upon initial election as a director and an option for 7,500 shares upon annual reelection. The chairman of the board will receive an option for 10,000 shares upon initial election as chairman, in addition to the option for 25,000 shares upon initial election as a director, and an option for 12,500 shares upon annual reelection. For more information, please see “Management—Stock Option and Other Compensation Plans—2005 Stock Incentive Plan.”

Executive Compensation

The following table sets forth other information regarding compensation awarded to, earned by or paid to our chief executive officer and our five other most highly compensated executive officers during 2003 and 2004. We refer to these officers in this prospectus as our named executive officers.

Summary Compensation Table

| Name and Principal Position | Year | Annual Compensation | | Long-Term Compensation | All Other Compensation |
|--|------|---------------------|--------|-------------------------------|------------------------|
| | | Salary | Bonus | Shares Underlying Options (#) | |
| J. Donald deBethizy, Ph.D. President and Chief Executive Officer | 2004 | \$ 283,250 | \$ (1) | — | \$ 13,000(3) |
| | 2003 | 275,000 | 66,000 | 1,969,332(2) | 12,000(3) |
| Merouane Bencherif, M.D., Ph.D. Vice President, Preclinical Research | 2004 | 170,000 | (1) | — | 12,518(3) |
| | 2003 | 161,000 | 38,640 | 585,623(2) | 11,485(3) |
| Jeffrey P. Brennan (4) Vice President, Business and Commercial Development | 2004 | 225,000 | (1) | — | 111,748(5) |
| | 2003 | 75,000 | 13,500 | 169,000(2) | 4,500(3) |
| William S. Caldwell, Ph.D. Vice President, Drug Discovery and Development | 2004 | 170,000 | (1) | — | 11,947(3) |
| | 2003 | 161,750 | 29,115 | 534,385(2) | 11,314(3) |
| Geoffrey C. Dunbar, Ph.D. Vice President, Clinical Development and Regulatory Affairs | 2004 | 254,150 | (1) | — | 13,000(3) |
| | 2003 | 246,750 | 44,415 | 668,396(2) | 12,000(3) |
| Alan A. Musso Vice President, Chief Financial Officer, Treasurer and Secretary | 2004 | 190,000 | (1) | — | 13,000(3) |
| | 2003 | 181,731(6) | 32,400 | 533,671(2) | 12,000(3) |

- (1) Bonuses earned for 2004 have not yet been determined. We intend to finalize the bonus amounts for our named executive officers in the first quarter of 2005. Bonus amounts will be determined by our board of directors based on our corporate performance.
- (2) A portion of these options reflects grants made on January 26, 2004 under our 2000 equity incentive plan in lieu of a cash bonus for fiscal year 2003. For information regarding these options, please see “—Stock Options,” below.

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- (3) Consists of our contributions under the Targacept Retirement Savings Plan, our 401(k) plan.
- (4) Mr. Brennan joined us in September 2003.
- (5) Consists of our contribution of \$12,190 under our 401(k) plan and reimbursement of \$99,558 in relocation expenses.
- (6) Salary amount includes compensation of \$1,731 in lieu of accrued vacation.

Stock Options

The following table sets forth information regarding grants of stock options to purchase shares of our common stock to our named executive officers during the year ended December 31, 2004.

The potential realizable values set forth in the following table are calculated based on the term of the option at the time of grant and reflect gains that could be achieved for the options if exercised at the end of the option term. The 5% and 10% assumed annual rates of compounded stock price appreciation are required by the Securities and Exchange Commission and do not represent our estimate or projection of our future stock price performance. Actual gains, if any, on stock option exercises depend on the future performance of the common stock and the date on which the options are exercised.

Option Grants in Last Fiscal Year

| Name | Number of Securities Underlying Options Granted | Percentage of Total Options Granted to Employees in Fiscal Year | Exercise Price Per Share | Expiration Date | Potential Realizable Value at Assumed Annual Rates of Stock Price Appreciation for Option Terms (2) | |
|---------------------------------|---|---|--------------------------|-----------------|---|-----|
| | | | | | 5% | 10% |
| J. Donald deBethizy, Ph.D. | 44,000 (1) | 9.0% | \$ 0.75 | 1/26/2014 | \$ | \$ |
| Merouane Bencherif, M.D., Ph.D. | — | — | — | — | | |
| Jeffrey P. Brennan | 9,000 (1) | 1.8 | 0.75 | 1/26/2014 | | |
| William S. Caldwell, Ph.D. | 19,410 (1) | 4.0 | 0.75 | 1/26/2014 | | |
| Geoffrey C. Dunbar, Ph.D. | 29,610 (1) | 6.1 | 0.75 | 1/26/2014 | | |
| Alan A. Musso | 21,600 (1) | 4.4 | 0.75 | 1/26/2014 | | |

- (1) These options reflect grants made on January 26, 2004 under our 2000 equity incentive plan in lieu of a cash bonus for fiscal year 2003 and were fully vested upon grant.
- (2) The dollar amounts under these columns are the result of rates set by the Securities and Exchange Commission and, therefore, are not intended to forecast possible future appreciation, if any, in the price of the underlying common stock. The potential realizable values at 5% and 10% appreciation are calculated using an estimated initial public offering price of \$ per share and assuming that the market price appreciates from this price at the indicated rate for the entire term of each option and that each option is exercised at the exercise price and sold on the last day of its term at the assumed appreciated price.

Option Exercises and Year-End Option Values

The following table sets forth information regarding the number of shares of our common stock issued upon option exercises by our named executive officers during the year ended December 31, 2004 and the value realized by our named executive officers. The table also sets forth information regarding the number and value of unexercised stock options held by our named executive officers as of December 31, 2004. There was no public trading market for our common stock as of December 31, 2004. Accordingly, as permitted by the rules of the Securities and Exchange Commission, we have calculated the value of the unexercised in-the-money options at fiscal year end by determining the difference between the exercise price per share and an assumed fair market value of our common stock as of December 31, 2004 equal to an assumed initial offering price of \$ per share, the mid-point of the estimated price range shown on the cover page of this prospectus.

Aggregated Option Exercises in Last Fiscal Year and Fiscal Year-End Option Values

| Name | Number of Shares Acquired on Exercise | Value Realized | Number of Securities Underlying Unexercised Options Held at December 31, 2004 | | Value of Unexercised In-the-Money Options at December 31, 2004 | |
|---------------------------------|---------------------------------------|----------------|---|---------------|--|---------------|
| | | | Exercisable | Unexercisable | Exercisable | Unexercisable |
| J. Donald deBethizy, Ph.D. | 399,174 | \$ 67,031 | 935,253 | 954,683 | \$ | \$ |
| Merouane Bencherif, M.D., Ph.D. | — | — | 514,848 | 274,470 | | |
| Jeffrey P. Brennan | — | — | 85,667 | 83,333 | | |
| William S. Caldwell, Ph.D. | — | — | 502,709 | 235,490 | | |
| Geoffrey C. Dunbar, Ph.D. | 169,522 | 11,867 | 379,521 | 308,580 | | |
| Alan A. Musso | 12,000 | 840 | 390,381 | 290,290 | | |

Employment Agreements

We have entered into employment agreements with each of our named executive officers. Each employment agreement continues until terminated by either party to the agreement, with the exception of Mr. Brennan's employment agreement, which is set to expire on December 31, 2007.

Under the terms of these employment agreements, Dr. deBethizy is employed as our Chief Executive Officer and President at a minimum annual base salary of \$225,000; Dr. Dunbar is employed as our Vice President, Clinical Development and Regulatory Affairs at a minimum annual base salary of \$246,750; Mr. Brennan is employed as our Vice President, Business and Commercial Development at a minimum annual base salary of \$225,000; Mr. Musso is employed as our Vice President and Chief Financial Officer at a minimum annual base salary of \$180,000; Dr. Bencherif is employed as our Vice President, Preclinical Research at a minimum annual base salary of \$135,000; and Dr. Caldwell is employed as our Vice President, Drug Discovery and Development at a minimum annual base salary of \$135,000. For 2005, the base salary of Dr. deBethizy is \$310,000; the base salary of Dr. Dunbar is \$264,316; the base salary of Mr. Brennan is \$234,000; the base salary of Mr. Musso is \$205,000; the base salary of Dr. Bencherif is \$200,000; and the base salary of Dr. Caldwell is \$185,000.

The employment agreements provide that the annual base salaries of each of the named executive officers will be reviewed and are subject to increase in accordance with our policies and procedures, and in addition, will be increased annually as necessary to be consistent with the median base salaries of employees in similar positions at comparable companies as described in the then current Radford Biotechnology Compensation Report.

In addition to annual base salary, each named executive officer is eligible to receive awards under our 2000 equity incentive plan and earn an annual bonus equal to a percentage of his annual base salary. The employment agreements provide that Dr. deBethizy is eligible to earn an annual bonus of up to 35% of his annual base salary; each of Dr. Dunbar and Mr. Brennan is eligible to earn an annual bonus of up to 30% of his annual base salary; and each of Mr. Musso and Drs. Bencherif and Caldwell is eligible to earn an annual bonus of up to 25% of his annual base salary. In 2001, our board of directors increased the annual bonus for Dr. deBethizy to up to 40% of his annual base salary. In 2002, our board of directors increased the annual bonus for each of Drs. Bencherif and Caldwell to up to 30% of his annual base salary and in 2003 increased the annual bonus for Mr. Musso to up to 30% of his annual base salary. Our board of directors or compensation committee, in their discretion, may increase the annual bonus for each named executive officer beyond these percentages.

Under the terms of the employment agreements, the named executive officers cannot disclose any of our proprietary information during the periods of their employment. In addition, the employment agreements prohibit the named executive officers from soliciting, on behalf of themselves or any entity other than us, any of our customers or clients for the period of employment and nine months following termination of employment, and in the case of Dr. deBethizy, one year following termination. Furthermore, any inventions, discoveries, improvements and developments made by the named executive officers during their employment with us become and remain our property.

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If a named executive officer's employment terminates for any reason, the named executive officer is entitled to receive a lump sum equal to any base salary, bonus and other compensation earned and due but not paid through the effective date of termination. In addition, if we terminate a named executive officer's employment other than for just cause or a named executive officer terminates his employment for good reason, in each case as that term is defined in his agreement, he is entitled to receive:

- severance, payable monthly, equal to his then current base salary for twelve months in the case of Dr. deBethizy and nine months for all other named executive officers, following termination or, if shorter, until he secures other employment;
- acceleration of unvested options to purchase capital stock or restricted stock – Dr. deBethizy is entitled to twelve months acceleration, Mr. Brennan is entitled to nine months acceleration and all other named executive officers are entitled to six months acceleration;
- continuation of the health and life insurance benefits coverage provided to him as of the date of termination for the period during which he receives severance; and
- up to \$10,000 in outplacement counseling services.

Stock Option and Other Compensation Plans

2000 Equity Incentive Plan

We maintain a 2000 equity incentive plan, which we refer to as our 2000 plan, that our board of directors and stockholders have approved. As of December 31, 2004, an aggregate of 9,216,657 shares of common stock had been authorized for issuance under our 2000 plan, of which options to purchase an aggregate of 7,408,736 shares of common stock were outstanding at a weighted average exercise price of \$0.65 per share, 97,500 shares of common stock were issued and outstanding in the form of restricted stock and 302,143 shares of common stock were available for future grant. Upon completion of this offering, 631,844 shares of common stock subject to unvested options outstanding as of December 31, 2004 will immediately vest.

Our 2000 plan provides for the grant of a variety of stock-based awards, including incentive stock options, nonqualified stock options, stock appreciation rights, performance awards and restricted stock, to our employees, directors, independent contractors, consultants and advisors.

Administration of the Plan. Our 2000 plan is administered by the compensation committee of our board of directors, which, among other things, determines the terms and recipients of grants under the 2000 plan.

Options. Recipients of stock options under our 2000 plan have the right to purchase a stated number of shares of common stock at a stated exercise price, subject to any other terms and conditions that may be stated in connection with the option grant. We may grant options at an exercise price equal to, less than or greater than the fair market value of our common stock on the date of grant, except that we may not grant incentive stock options and options intended to qualify as performance-based compensation under Section 422 of the Internal Revenue Code to optionees holding more than 10% of the voting power of all shares of our capital stock at an exercise price less than 110% of the fair market value of our common stock on the date of grant. Grant recipients may pay the exercise price of stock options by various methods permitted under our 2000 plan. Unless modified with respect to any particular grant:

- an employee who is terminated for any reason other than death, disability or cause will have 90 days to exercise options vested as of the termination date;
- an employee who terminates due to death or disability will have one year, or until the end of the respective option periods, if sooner, to exercise options that are vested as of the termination date;
- an employee who is terminated for cause will forfeit all options immediately upon termination; and
- non-employee optionees who are terminated will have 90 days, or until the end of the respective option periods, if sooner, to exercise options that are vested as of the termination date unless service terminates for cause, in which case the options terminate immediately.

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Stock Awards. We may grant stock awards to participants subject to certain restrictions or no restrictions. Until they are vested and earned, unless an individual award agreement provides otherwise, grantees will not have the right to vote shares of restricted stock or the right to receive dividends or other distributions paid on such shares. If a grantee's employment or other service terminates during the restriction period or if any other conditions are not met, the restricted stock still subject to restrictions will terminate, unless an individual award agreement provides otherwise, and the shares must be immediately returned to us.

Significant Transactions. If:

- any entity or person acquires 50% or more of our outstanding common stock or, if such person owned shares as of August 22, 2000, 67% of our outstanding common stock; or
- our stockholders approve a sale or disposition of all or substantially all of our assets or a merger or consolidation in which we would not be the surviving or continuing corporation or which would result in the conversion of our common stock into cash, securities or other property (other than a merger or consolidation in which holders of common stock immediately prior to the merger or consolidation have the same proportionate ownership of common stock of the surviving corporation immediately after the merger as immediately before),

all awards outstanding under our 2000 plan would become immediately vested and exercisable unless, in the case of a merger, consolidation, share exchange or asset sale or disposition, the board of directors or compensation committee determines that outstanding awards will not become immediately vested and exercisable because steps have been taken, such as the assumption of the awards or substitution of substantially equivalent awards by the other party, as it deems equitable to protect the rights of participants in our 2000 plan. Upon completion of this offering, all awards outstanding under our 2000 plan granted prior to August 20, 2003 would become immediately vested and exercisable.

Termination and Amendment. We may grant awards under our 2000 plan until August 21, 2010, unless our 2000 plan is terminated prior to that date. The board of directors may amend or terminate our 2000 plan at any time, subject to the rights of holders of outstanding awards. Our 2005 stock incentive plan, which we refer to as our 2005 plan, is intended to serve as the successor equity incentive program to our 2000 plan. However, our board of directors may not amend our 2000 plan without stockholder approval if stockholder approval is required in order for grants of incentive stock options to meet the requirements of Section 422 of the Internal Revenue Code, or if stockholder approval is required in order to exempt compensation under our 2000 plan from the deduction limit under Section 162(m) of the Internal Revenue Code.

2005 Stock Incentive Plan

Introduction. Our 2005 plan is intended to serve as the successor equity incentive program to our 2000 plan. Our 2005 plan will become effective on the day prior to the date that the underwriting agreement for this offering is signed. At that time, all of the shares reserved for grant under our 2000 plan will be transferred to our 2005 plan and no further options will be granted under our 2000 plan.

Subject to adjustments as provided in our 2005 plan, the maximum number of shares that we may issue pursuant to awards granted under our 2005 plan may not exceed the sum of (i) _____ shares and (ii) up to _____ shares of common stock (a) remaining available for issuance as of the effective date under our 2000 plan or any other employee stock incentive plan that we maintain prior to the effective date and/or (b) subject to an award granted under our 2000 plan or any other prior plan, which award is forfeited, cancelled, terminated, expires or lapses for any reason, without the issuance of shares pursuant to the award. The maximum number of shares of common stock that we may issue under our 2005 plan pursuant to the grant of (i) incentive stock options is _____ and (ii) restricted awards is _____. In any calendar year, (i) we may not grant to any participant options and stock appreciation rights, or SARs, that are not related to an option for more than _____ shares of common stock; (ii) we may not grant to any participant awards for more than _____ shares of common stock; and (iii) participants may not receive awards paid in cash having an

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aggregate dollar value in excess of \$ _____, subject to adjustments as provided in our 2005 plan. For purposes of these restrictions, we will treat an option and related SAR as a single award. The following will not be included in calculating the share limitations set forth above: (i) dividends, including dividends paid in shares of common stock, or dividend equivalents paid in cash in connection with outstanding awards; (ii) awards which by their terms are settled in cash rather than the issuance of shares; (iii) any shares subject to an award under our 2005 plan that is forfeited, cancelled, terminated, expires or lapses for any reason without the issuance of shares underlying the award; and (iv) any shares a participant surrenders or we withhold to pay the option or purchase price for an award or use to satisfy any tax withholding requirement in connection with the exercise, vesting or earning of an award if, in accordance with the terms of our 2005 plan, a participant pays such option or purchase price or satisfies such tax withholding by either tendering previously owned shares or having us withhold shares.

We may adjust the number of shares reserved for issuance under our 2005 plan and the terms of awards in the event of an adjustment in our capital stock structure or one of our affiliates due to a merger, stock split, stock dividend or similar event.

Purpose and Eligibility. The purpose of our 2005 plan is to encourage and enable selected employees and our directors and independent contractors to acquire or increase their holdings of common stock and other proprietary interests in us in order to promote a closer identification of their interests with those of us and our stockholders, thereby further stimulating their efforts to enhance our efficiency, soundness, profitability, growth and stockholder value. The purpose will be carried out by the granting of awards to selected participants. We may grant awards under our 2005 plan which include incentive stock options and nonqualified stock options; SARs; restricted awards in the form of restricted stock awards and restricted stock units; performance awards in the form of performance shares and performance units; phantom stock awards; director options in the form of initial options and annual options; and dividend equivalent awards. We discuss the material terms of each type of award below.

Administration; Amendment and Termination. Our board of directors, or upon its delegation, the compensation committee of our board of directors, will administer our 2005 plan. In this discussion, we refer to our board of directors and the compensation committee collectively as the administrator. Under the terms of our 2005 plan, the administrator has full and final authority to take any action with respect to our 2005 plan, including, without limitation, the authority to: (i) determine all matters relating to awards, including selection of individuals to be granted awards, the types of awards, the number of shares, if any, of common stock subject to an award, and the terms, conditions, restrictions and limitations of an award; (ii) prescribe the form or forms of agreements evidencing awards granted under our 2005 plan; (iii) establish, amend and rescind rules and regulations for the administration of our 2005 plan; and (iv) construe and interpret our 2005 plan, awards and award agreements made under the 2005 plan, interpret rules and regulations for administering the 2005 plan and make all other determinations deemed necessary or advisable for administering the 2005 plan.

In certain circumstances and subject to certain terms and conditions, the administrator may delegate to one or more of our officers the authority to grant awards, and to make any or all of the determinations reserved for the administrator in our 2005 plan with respect to such awards.

Our board of directors may amend, alter or terminate our 2005 plan at any time, subject to the following: (i) stockholder approval is required of any amendment if such approval is required by applicable law, rule or regulation; and (ii) except for anti-dilution adjustments made under our 2005 plan, the option price for any outstanding option or base price of any outstanding SAR may not be decreased after the date of grant, nor may any participant surrender any outstanding option or SAR to us as consideration for the grant of a new option or SAR with a lower option or base price than the original option or SAR, as the case may be, without stockholder approval of any such action.

The administrator has the authority to make adjustments to awards upon the occurrence of certain unusual or nonrecurring events, if the administrator determines that such adjustments are appropriate in order to prevent dilution or enlargement of the benefits or potential benefits intended to be made available under our 2005 plan or

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necessary or appropriate to comply with applicable laws, rules or regulations. The administrator may cause any award or any portion of an award granted under our 2005 plan to be cancelled in consideration of an alternative award or cash payment of an equivalent cash value, as determined by the administrator, made to the holder of the cancelled award. The administrator also may determine, in its discretion, that a participant's rights, payments and/or benefits with respect to an award, including but not limited to any shares issued or issuable and/or cash paid or payable with respect to an award, will be subject to reduction, cancellation, forfeiture or recoupment upon the occurrence of certain specified events, in addition to any otherwise applicable vesting or performance conditions of an award.

Options. Our 2005 plan authorizes the grant of both incentive stock options and nonqualified stock options, both of which are exercisable for shares of common stock, although incentive stock options may only be granted to our employees. The administrator will determine the option price at which a participant may exercise an option and the option price must be:

- with respect to incentive stock options, no less than 100% of the fair market value per share of our common stock on the date of grant, or 110% of the fair market value with respect to incentive stock options granted to an employee who owns stock and who possesses more than 10% of the total voting power of all classes of our stock or stock of our parent or subsidiary corporation, if any;
- with respect to nonqualified stock options, no less than 85% of the fair market value per share of our common stock on the date of grant; and
- not less than the par value per share of our common stock.

Unless an individual award agreement provides otherwise, a participant may pay the option price in the form of cash or cash equivalent; in addition, where the administrator and applicable laws, rules and regulations permit, a participant may also make payment:

- by delivery of shares of common stock the participant has owned for at least six months or for such other time period that the administrator determines and which is otherwise acceptable to the administrator;
- by shares of common stock withheld upon exercise;
- with respect only to purchase upon exercise of an option after a public market for the common stock exists, by delivery of written notice of exercise to us and delivery to a broker of written notice of exercise and irrevocable instructions to promptly deliver to us the amount of sale or loan proceeds to pay the option price;
- by such other payment methods as the administrator may approve and which are acceptable under applicable law; or
- by any combination of these methods.

At the time of option grant, the administrator will determine the term and conditions of an option and the period or periods during which a participant may exercise an option and, in the case of incentive stock options, the option term may not exceed 10 years, or five years with respect to an employee who owns stock and who possesses more than 10% of the total combined voting power of all classes of our stock or stock of our parent or subsidiary corporation, if any. Options are also subject to certain restrictions on exercise if the participant terminates employment. The administrator has authority to establish other terms and conditions related to options.

Director Options. Each non-employee director who is first elected or appointed to our board of directors after the public offering date will receive an initial option to purchase 25,000 shares of common stock on the fifth business day after such director is first elected or appointed to our board of directors. A non-employee director who is first elected or appointed as chairman of the board also will receive an initial option for 10,000 shares. In addition, we will grant to each non-employee director, on an annual basis commencing with the 2005 annual meeting of stockholders, a director option to purchase 7,500 shares of common stock or, in the case of the

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chairman of the board, a director option to purchase 12,500 shares. This annual option will be granted to a director upon his or her reelection to the board on the fifth business day after the applicable annual or other stockholders meeting, provided that such director continues to serve as a member of our board of directors as of such grant date. Director options will be designated as nonqualified options. The option price at which a director may exercise a director option will be 100% of the fair market value per share of the common stock on the date the option is granted. Each initial option will vest and become exercisable on the first anniversary of the date of grant with respect to one-third of the shares subject to the option. Each initial option will vest with respect to the remaining two-thirds of the shares subject to the option on a pro rata quarterly basis over the next two years, so that the option will be vested in full as of the third anniversary of the date of grant if the director continues in service during such period. Each annual option will vest in full on the first anniversary of the date of grant. The term of a director option may not exceed 10 years from the date of grant. Director options are also subject to certain restrictions on exercise if the director's service on our board of directors terminates. The administrator also has authority to establish other terms and conditions related to director options.

Stock Appreciation Rights. Under the terms of our 2005 plan, we may grant SARs to the holder of an option with respect to all or a portion of the shares of common stock subject to the option or we may grant SARs separately. The holder of an SAR may receive consideration paid either (i) in cash; (ii) shares of common stock valued at fair market value on the date of the SAR exercise; or (iii) a combination of cash and shares of common stock, as the administrator determines. Upon exercise of an SAR, a participant is entitled to receive from us consideration in an amount determined by multiplying:

- the difference between the fair market value of a share of common stock on the date of exercise of the SAR over the base price of the SAR by
- the number of shares of common stock with respect to which the SAR is being exercised.

Notwithstanding the foregoing, the administrator may limit the amount payable in its discretion. The base price may be no less than 100% of the fair market value per share of the common stock on the date the SAR is granted. We may pay consideration upon exercise of an SAR currently or on a deferred basis.

SARs are exercisable according to the terms established by the administrator and stated in the applicable award agreement. Upon the exercise of an SAR granted to the holder of an option, the option is deemed to be cancelled to the extent of the number of shares as to which the holder of an option exercises the SAR. No participant may exercise an SAR more than 10 years after it was granted, or such shorter period as may apply to related options. Each award agreement will set forth the extent to which the holder of an SAR will have the right to exercise an SAR following termination of the holder's employment or service with us.

Restricted Awards. Subject to the limitations of our 2005 plan, the administrator may in its sole discretion grant restricted awards to such individuals in such numbers, upon such terms and at such times as the administrator shall determine. Restricted awards may be in the form of restricted stock awards and/or restricted stock units that are subject to certain conditions, which conditions must be met in order for the restricted award to vest and be earned, in whole or in part, and no longer subject to forfeiture. Restricted stock awards may be payable in shares of common stock. Restricted stock units may be payable in cash or whole shares of common stock, or partly in cash and partly in whole shares of common stock, in accordance with the terms of our 2005 plan and the discretion of the administrator.

The administrator has authority to determine the nature, length and starting date of the period during which a participant may earn a restricted award and will determine the conditions that must be met in order for a restricted award to be granted or to vest or be earned. These conditions may include:

- payment of a stipulated purchase price;
- attainment of performance objectives;
- continued service or employment for a certain period of time or a combination of attainment of performance objectives and continued service;

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- retirement;
- displacement;
- disability;
- death; or
- any combination of such conditions.

However, restricted awards that vest based solely on continued service or the passage of time will be subject to a minimum restriction period of one year, except in the case of restricted awards assumed or substituted in connection with mergers or other business transactions, restricted awards granted in connection with hiring a participant and/or restricted awards granted under an incentive compensation or bonus program.

In the case of restricted awards based upon performance criteria, or a combination of performance criteria and continued service, the administrator will determine the performance measures applicable to such restricted awards, which performance measures may be based upon such corporate, business unit or division and/or individual performance factors and criteria as the administrator in its discretion may deem appropriate; provided, however, that such performance factors will be limited to the specific performance measures listed below.

The administrator has authority to determine whether and to what degree restricted awards have vested and been earned and are payable. If a participant's employment or service is terminated for any reason and all or any part of a restricted award has not vested or been earned pursuant to the terms of our 2005 plan and the individual award, the participant will forfeit the award unless the administrator determines otherwise.

Performance Awards. Subject to the limitations of our 2005 plan, the administrator may in its discretion grant performance awards to such eligible individuals upon such terms and conditions and at such times as the administrator shall determine. Performance awards may be in the form of performance shares and/or performance units. An award of a performance share is a grant of a right to receive shares of our common stock, the cash value thereof or a combination thereof in the administrator's discretion, which is contingent upon the achievement of performance or other objectives during a specified period and which has a value on the date of grant equal to the fair market value of a share of our common stock. An award of a performance unit is a grant of a right to receive shares of our common stock or a designated dollar value amount of common stock that is contingent upon the achievement of performance or other objectives during a specified period, and that has an initial value determined in a dollar amount established by the administrator at the time of grant.

The administrator has the authority to determine the nature, length and starting date of the period during which a participant may earn a performance award and will determine the conditions that must be met in order for a performance award to be granted or to vest or be earned. These conditions may include specific performance objectives, continued service or employment for a certain period of time, or a combination of such conditions. In the case of performance awards based on performance criteria, the administrator will determine the performance measures applicable to such awards, which performance measures may be based upon such corporate, business unit or division and/or individual performance factors and criteria as the administrator in its discretion may deem appropriate; provided, however, that such performance factors will be limited to the specific performance measures listed below.

The administrator has authority to determine whether and to what degree performance awards have been earned and are payable. If a participant's employment or service is terminated for any reason and all or part of a performance award has not been earned pursuant to the terms of our 2005 plan and the individual award agreement, the participant will forfeit the award unless the administrator determines otherwise.

Phantom Stock Awards. Subject to the limitations of our 2005 plan, the administrator may in its discretion grant phantom stock awards to such eligible individuals in such numbers, upon such terms and at such times as the administrator shall determine. An award of phantom stock is an award of a number of hypothetical share units with respect to shares of our common stock, with a value based on the fair market value of a share of common stock.

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The administrator has the authority to determine whether and to what degree phantom stock awards have vested and are payable. Upon vesting of all or part of a phantom stock award and satisfaction of other terms and conditions that the administrator determines, the holder of a phantom stock award will be entitled to a payment of an amount equal to the fair market value of one share of our common stock with respect to each such phantom stock unit that has vested. We may make payment in cash, shares of common stock, or a combination of cash and stock, as determined by the administrator. The administrator may determine the forms and terms of payment of phantom stock awards in accordance with our 2005 plan. If a participant's employment or service is terminated for any reason and all or any part of a phantom stock award has not vested and become payable pursuant to the terms of our 2005 plan and the individual award, the participant will forfeit the award unless the administrator determines otherwise.

Dividend and Dividend Equivalents. The administrator may, in its sole discretion, provide that awards granted under our 2005 plan earn dividends or dividend equivalents. We may pay such dividends or dividend equivalents currently or credit such dividends or dividend equivalents to a participant's account, subject to such restrictions and conditions as the administrator may establish with respect to the crediting of an account, including reinvestment in additional shares of common stock or share equivalents.

Change in Control. Upon a change in control as defined in our 2005 plan, and unless an award agreement provides otherwise, our 2005 plan provides that: (i) all options and SARs outstanding as of the date of the change in control will become fully exercisable, whether or not then otherwise exercisable; and (ii) any restrictions applicable to any restricted award, performance award and/or phantom stock award will be deemed to have been met, and such awards will become fully vested, earned and payable to the fullest extent of the original grant of the applicable award. However, our 2005 plan authorizes the administrator, in the event of a merger, share exchange, reorganization, sale of all or substantially all of our assets or other similar transaction or event affecting us or one of our affiliates or stockholders, to determine that any or all awards will not vest or become exercisable on an accelerated basis, if we or the surviving or acquiring corporation takes action, including but not limited to the assumption of awards or the grant of substitute awards, that, in the opinion of the administrator, is equitable or appropriate to protect the rights and interest of participants under our 2005 plan.

Transferability. Incentive stock options are not transferable other than by will or the laws of intestate succession or, in the administrator's discretion, as may otherwise be permitted in accordance with Section 422 of the Internal Revenue Code and related regulations. Nonqualified stock options, director options and SARs are not transferable other than by will or the laws of intestate succession, except as permitted by the administrator in a manner consistent with the registration provisions of the Securities Act. Restricted awards, performance awards and phantom stock awards that have not vested and been earned are not transferable, including by sale, assignment, pledge or hypothecation, other than by will or the laws of intestate succession, and participants may not sell, transfer, assign, pledge or otherwise encumber shares subject to such awards until the restriction period and/or performance period has expired and until all conditions to vesting and/or earning the award have been met.

General Federal Income Tax Consequences. Under current federal laws, in general, recipients of awards and grants of nonqualified stock options, SARs, restricted stock, dividend equivalents, performance awards and stock payments under our 2005 plan are taxable under Section 83 of the Internal Revenue Code upon their receipt of common stock or cash with respect to such awards or grants and, subject to Section 162(m) of the Internal Revenue Code and certain reporting requirements, we will be entitled to an income tax deduction with respect to the amounts taxable as ordinary income to such recipients. Under Sections 421 and 422 of the Internal Revenue Code, recipients of incentive stock options are generally not taxed on their receipt of common stock upon their exercises of incentive stock options if the option stock is held for specified minimum holding periods and, in such event, we would not be entitled to income tax deductions with respect to such exercises.

Performance-Based Compensation—Section 162(m) Requirements. Our 2005 plan is structured to comply with the requirements imposed by Section 162(m) of the Internal Revenue Code and related regulations in order to preserve, to the extent practicable, our tax deduction for awards made under our 2005 plan to covered

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employees. Section 162(m) of the Internal Revenue Code generally denies an employer a deduction for compensation paid to covered employees, which are generally the named executive officers, of a publicly held corporation in excess of \$1,000,000 unless the compensation is exempt from the \$1,000,000 limitation because it is performance-based compensation.

In order to qualify as performance-based compensation, we must pay the compensation under our 2005 plan to covered employees under pre-established objective performance goals that a committee comprised of outside directors determines and certifies. In addition to other requirements for the performance-based exception, we must advise stockholders, and stockholders must approve, the material terms or changes in material terms of the performance goals under which compensation is to be paid. Material terms include the individuals eligible to receive compensation, a description of the business criteria on which the performance goals are based, and either the maximum amount of the compensation to be paid or the formula used to calculate the amount of compensation if the performance goals are met.

As proposed, our 2005 plan limits the maximum amount of awards that we may grant to any employee. In particular, in any calendar year, (i) we may not grant to any participant options and SARs that are not related to an option for more than _____ shares of common stock; (ii) we may not grant to any participant awards for more than _____ shares of common stock; and (iii) no participant may receive awards paid in cash having an aggregate dollar value in excess of \$ _____. Further, with respect to performance-based restricted awards and performance awards, and in some cases, certain other types of awards, payable to covered employees that are intended to be eligible for the compensation limitation exception available under Section 162(m) and related regulations, our 2005 plan limits performance measures to one or more of the following: cash flow, return on equity, return on assets, earnings per share, achievement of clinical development or regulatory milestones, operations expense efficiency milestones, consolidated earnings before or after taxes and including earnings before interest, taxes, depreciation and amortization, net income, operating income, book value per share, return on investment, return on capital, improvements in capital structure, expense management, profitability of an identifiable business unit or product, maintenance or improvement of profit margins, stock price or total stockholder return, market share, revenues or sales, costs, working capital, economic wealth created, strategic business criteria, efficiency ratios, achievement of division, group, function or corporate financial, strategic or operational goals and comparisons with stock market indices or performances of metrics of peer companies.

To the extent that Section 162(m) of the Internal Revenue Code is applicable, the administrator will, within the time and in the manner prescribed by Section 162(m) of the Internal Revenue Code and related regulations, define in an objective fashion the manner of calculating the performance measures it selects to use for participants during any specific performance period. We may adjust or modify such performance factors due to extraordinary items, transactions, events or developments, or in recognition of, or in anticipation of, any other unusual or nonrecurring events affecting us or our financial statements, or in response to, or in anticipation of, changes in applicable laws, regulations, accounting principles or business conditions, in each case as the administrator may determine.

Targacept Retirement Savings Plan—401(k) Plan

Our employees are eligible to participate in our 401(k) plan. Under our 401(k) plan, eligible employees may elect to make a salary reduction contribution up to the statutorily prescribed annual limit. The 401(k) plan is intended to qualify under Section 401 of the Internal Revenue Code, so that the contributions by our employees will be deductible when made and income earned on 401(k) plan contributions will not be taxable to our employees until withdrawals are made. We match the contributions of our eligible employees at up to a maximum of 6% of an eligible employee's salary.

Limitation of Liability and Indemnification

Our certificate of incorporation includes a provision that eliminates the personal liability of our directors for monetary damages to the fullest extent permitted by Section 102(b)(7) of the Delaware General Corporation Law. Under that statute, a director's liability for monetary damages to us or our stockholders may not be limited with respect to:

- a breach of the director's duty of loyalty to us or our stockholders;
- an act or omission not in good faith or involving intentional misconduct or a knowing violation of law;
- an improper distribution to stockholders; or
- a transaction from which the director derived an improper personal benefit.

Our bylaws provide that we will indemnify and hold harmless any person who is made or threatened to be made a party to any matter because he or she is or was our director or officer or was serving as a director, officer or trustee of another entity, employee benefit plan or enterprise at our request to the fullest extent permitted by the Delaware General Corporation Law. Prior to the completion of this offering, we plan to enter into agreements to indemnify our directors and officers. These agreements, among other things, will indemnify our directors and officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by any such person in any action or proceeding, including any action by us arising out of such person's services as our director or officer, any of our subsidiaries from time to time or any other company or enterprise to which the person provides services at our request. We believe that these provisions and agreements are necessary to attract and retain qualified persons as directors and officers. Currently, there is no pending litigation or proceeding involving any of our directors, officers or employees for which indemnification is sought, nor are we aware of any threatened litigation that may result in claims for indemnification. We currently maintain directors' and officers' liability insurance for each of our directors and officers.

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Since August 22, 2000, we have engaged in the following transactions with our directors and executive officers and holders of more than 5% of our voting securities and affiliates of our directors, executive officers and 5% stockholders.

Stock Issuances

Issuance of Common Stock

On August 22, 2000, at the time that we became an independent company, we issued and sold an aggregate of 309,424 shares of our common stock for an aggregate purchase price of approximately \$309. The following table sets forth the number of shares of common stock sold to our founders.

| <u>Name</u> | <u>Number of Shares of Common Stock</u> | <u>Aggregate Purchase Price</u> |
|---------------------------------|---|-------------------------------------|
| J. Donald deBethizy, Ph.D. | 135,373 | \$ 135 |
| Merouane Bencherif, M.D., Ph.D. | 58,017 | 58 |
| William S. Caldwell, Ph.D. | 58,017 | 58 |
| Patrick M. Lippiello, Ph.D. | 58,017 | 58 |

On August 8, 2002, we issued 47,500 shares of restricted stock to Mr. Skaletsky for an aggregate purchase price of \$475. On June 11, 2003, we issued 12,500 shares of restricted stock to Mr. Skaletsky for an aggregate purchase price of \$125. On October 15, 2004, we issued 12,500 shares of restricted stock to Mr. Skaletsky for an aggregate purchase price of \$125.

On April 18, 2003, we issued 25,000 shares of restricted stock to Mr. Richard for an aggregate purchase price of \$250.

Issuance of Series A Convertible Preferred Stock

On August 22, 2000, we recapitalized our 500 outstanding shares of common stock held by R.J. Reynolds Tobacco Company, our then parent corporation, into 5,000,000 shares of series A convertible preferred stock and a warrant to purchase 1,612,903 shares of common stock at an exercise price of \$4.65 per share. As a result of price protection provisions contained in the warrant, the exercise price was reduced to \$1.95 per share upon our issuance of shares of series C convertible preferred stock in November 2002 and March 2003. All of the shares of series A convertible preferred stock and the warrant were subsequently assigned to R.J. Reynolds Tobacco Holdings, Inc. Each share of series A convertible preferred stock will convert into one share of common stock concurrently with the completion of this offering. The warrant will be cancelled if it is not exercised prior to the completion of this offering. If R.J. Reynolds exercises the warrant in full for cash, we would issue 1,612,903 shares of common stock and receive cash proceeds of approximately \$3.1 million. If R.J. Reynolds exercises the warrant on a cashless basis, we would issue _____ shares of common stock, based on an assumed initial public offering price of \$ _____ per share.

Mr. Blixt, one of our directors, is the executive vice president and general counsel of R.J. Reynolds Tobacco Company and is executive vice president, general counsel and assistant secretary of its parent company, R.J. Reynolds Tobacco Holdings, Inc.

Issuance of Series B Convertible Preferred Stock

On August 22, November 30, December 5 and December 19, 2000, we issued and sold an aggregate of 6,537,634 shares of our series B convertible preferred stock at a purchase price per share of \$4.65 for an aggregate purchase price of approximately \$30.4 million. On January 26, 2001, we issued an additional 29,933 shares of our series B convertible preferred stock in partial satisfaction of an outstanding payment obligation.

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The following table sets forth the aggregate number of shares of series B convertible preferred stock sold to our 5% stockholders and their affiliates on August 22, November 30, December 5 and December 19, 2000.

| <u>Name</u> | <u>Number of Shares of Series B Preferred Stock</u> | <u>Aggregate Purchase Price</u> |
|--|---|-------------------------------------|
| Entities affiliated with EuclidSR Partners, L.P. | 2,021,505 | \$ 9,399,998 |
| Entities affiliated with Burrill & Company LLC | 1,075,269 | 5,000,001 |
| Entities affiliated with Advent Private Equity Fund II | 1,075,269 | 5,000,001 |

These shares of our series B convertible preferred stock will convert into an aggregate of 9,948,718 shares of our common stock concurrently with the completion of this offering.

Dr. Jones, one of our directors, is a general partner of EuclidSR Associates, L.P., the general partner of EuclidSR Partners, L.P. Mr. Burrill, one of our directors, is the chief executive officer of Burrill & Company LLC.

Issuances of Series C Convertible Preferred Stock

On November 26, 2002 and March 14, 2003, we issued and sold an aggregate of 49,169,138 shares of our series C convertible preferred stock at a purchase price per share of \$1.21 for an aggregate purchase price of approximately \$59.5 million. The following table sets forth the aggregate number of shares of series C convertible preferred stock sold to our 5% stockholders and their affiliates on November 26, 2002 and March 14, 2003.

| <u>Name</u> | <u>Number of Shares of Series C Preferred Stock</u> | <u>Aggregate Purchase Price</u> |
|--|---|-------------------------------------|
| Entities affiliated with New Enterprise Associates | 12,396,694 | \$ 15,000,000 |
| Nomura International plc | 8,264,462 | 9,999,999 |
| Entities affiliated with Oxford Bioscience Partners | 6,198,347 | 7,500,000 |
| Entities affiliated with EuclidSR Partners, L.P. | 5,123,966 | 6,199,999 |
| Entities affiliated with Burrill & Company LLC | 1,540,440 | 1,863,932 |
| Entities affiliated with Advent Private Equity Fund II | 1,540,440 | 1,863,932 |

These shares of our series C convertible preferred stock will convert into an aggregate of 37,882,020 shares of our common stock concurrently with the completion of this offering.

On December 6, 2004, we issued and sold an aggregate of 27,272,728 additional shares of our series C convertible preferred stock at a purchase price per share of \$1.21 for an aggregate purchase price of approximately \$33.0 million. The following table sets forth the number of shares of series C convertible preferred stock sold to our 5% stockholders and their affiliates on December 6, 2004.

| <u>Name</u> | <u>Number of Shares of Series C Preferred Stock</u> | <u>Aggregate Purchase Price</u> |
|--|---|-------------------------------------|
| New Enterprise Associates 10, Limited Partnership | 7,851,240 | \$ 9,500,000 |
| Nomura Phase4 Ventures LP | 6,570,248 | 7,950,000 |
| EuclidSR Partners, L.P. | 3,471,074 | 4,200,000 |
| Burrill Biotechnology Capital Fund, L.P. | 1,487,603 | 1,800,000 |
| Entities affiliated with Advent Private Equity Fund II | 1,033,058 | 1,250,000 |
| R.J. Reynolds Tobacco Holdings, Inc. | 1,652,893 | 2,000,000 |

These shares of our series C convertible preferred stock will convert into an aggregate of 23,839,285 shares of our common stock concurrently with the completion of this offering.

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Dr. Barrett, one of our directors, is a general partner of NEA Partners 10, Limited Partnership, the general partner of New Enterprise Associates 10, Limited Partnership, which is an affiliate of New Enterprise Associates. Dr. Walton, one of our directors, is a general partner of OBP Management IV L.P., the general partner of Oxford Bioscience Partners IV L.P., which is an affiliate of Oxford Bioscience Partners.

Registration Rights

Pursuant to the terms of an investor rights agreement that we entered into with the holders of our series A, series B and series C convertible preferred stock on November 26, 2002, we granted registration rights to these holders. For a more detailed description of these registration rights, see “Description of Capital Stock—Registration Rights.”

Loan Agreement with R.J. Reynolds Tobacco Holdings, Inc.

In May 2002, we borrowed \$2.5 million from R.J. Reynolds Tobacco Holdings, Inc. to finance equipment and other fixed assets. The borrowing bears a fixed interest rate of 6.6%, is payable in 48 equal monthly installments and matures in May 2006. In January 2004, we amended the terms of our loan facility to permit us to borrow up to an additional \$2.0 million in 2004 in up to three separate borrowings. Each borrowing would bear a fixed interest rate equal to a theoretical four-year U.S. Treasury Rate on the disbursement date plus 3.5%, be payable in 48 equal monthly installments and be secured by specified tangible fixed assets that R.J. Reynolds determined to be sufficient at the time of disbursement. We borrowed \$1.0 million in April 2004 and \$973,000 in December 2004 under the amended loan facility to finance equipment. The April 2004 borrowing bears a fixed interest rate of 5.9%, is payable in 48 equal monthly installments and matures in April 2008. The December 2004 borrowing bears a fixed interest rate of 6.9%, is payable in 48 equal monthly installments and matures in January 2009. All borrowings under the loan facility are secured by specified tangible fixed assets. We believe that the terms of the loan facility are no less favorable than those that we could have obtained from an unaffiliated third party. As of December 31, 2004, the outstanding principal balance under the loan facility was \$2.8 million.

Payments to R.J. Reynolds Tobacco Company

Prior to December 31, 2003, we used the services of an R.J. Reynolds Tobacco Company employee for toxicology studies and purchased materials used for research and development and copy and printing services through R.J. Reynolds Tobacco Company. We paid \$201,000 for these services during 2003. During the nine months ended September 30, 2004, we continued to use only the copy and printing services and paid \$39,000 for these services.

Director Compensation

For information regarding stock options granted to our non-employee directors, see “Management—Director Compensation.”

Executive Compensation and Employment Agreements

For information regarding the compensation of our executive officers, see “Management—Executive Compensation” and “—Stock Options.” For information regarding employment agreements with our executive officers, see “Management—Employment Agreements.”

PRINCIPAL STOCKHOLDERS

The following table sets forth information regarding the beneficial ownership of our common stock as of December 31, 2004 and on an as adjusted basis to reflect the sale of the common stock offered in this offering by:

- each of our directors;
- each of our named executive officers;
- each person known by us to beneficially own 5% or more of our common stock; and
- all of our directors and executive officers as a group.

The number of shares of common stock beneficially owned by each stockholder is determined under rules issued by the Securities and Exchange Commission and includes voting or investment power with respect to securities. Under these rules, beneficial ownership includes any shares as to which the individual or entity has sole or shared voting power or investment power and includes any shares that an individual or entity has the right to acquire beneficial ownership of within 60 days of December 31, 2004 through the exercise of any warrant, stock option or other right. Unless otherwise indicated, the address of all listed stockholders is c/o Targacept, Inc., 200 East First Street, Suite 300, Winston-Salem, North Carolina 27101. Each of the stockholders listed has sole voting and investment power with respect to the shares beneficially owned by the stockholder unless noted otherwise, subject to community property laws where applicable.

| Name and Address of Beneficial Owner | Number of Shares Beneficially Owned | Percentage of Shares Beneficially Owned (1) | |
|--|-------------------------------------|---|----------------|
| | | Before Offering | After Offering |
| 5% Stockholders | 21,907,500 | 20.8% | |
| Entities affiliated with New Enterprise Associates (2) 1119 St. Paul Street Baltimore, Maryland 21202 | | | |
| Entities affiliated with EuclidSR Partners, L.P. (3) 45 Rockefeller Plaza, Suite 3240 New York, New York 10111 | 14,146,226 | 13.5% | |
| Entities affiliated with Nomura Phase4 Ventures Limited (4) Nomura House 1 St. Martin's-le-Grand London EC1A 4NP England | 16,026,785 | 15.2% | |
| Entities affiliated with Oxford Bioscience Partners (5) 222 Berkeley Street, Suite 1650 Boston, Massachusetts 02116 | 6,728,928 | 6.4% | |
| R.J. Reynolds Tobacco Holdings, Inc. (6) 401 North Main Street Winston-Salem, North Carolina 27102 | 8,455,342 | 7.9% | |
| Entities affiliated with Burrill & Company LLC (7) One Embarcadero Center, Suite 2700 San Francisco, California 94111 | 5,875,471 | 5.6% | |
| Entities affiliated with Advent Private Equity Fund II (8) 25 Buckingham Gate London SW1E 6LD England | 5,344,399 | 5.1% | |

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| Name and Address of Beneficial Owner | Number of Shares Beneficially Owned | Percentage of Shares Beneficially Owned (1) | |
|---|-------------------------------------|---|----------------|
| | | Before Offering | After Offering |
| Executive Officers and Directors | | | |
| J. Donald deBethizy, Ph.D. (9) | 1,732,767 | 1.6% | |
| Merouane Bencherif, M.D., Ph.D. (10) | 617,865 | * | |
| Jeffrey P. Brennan (11) | 85,667 | * | |
| William S. Caldwell, Ph.D. (12) | 605,726 | * | |
| Geoffrey C. Dunbar, M.D. (13) | 613,106 | * | |
| Alan A. Musso (14) | 506,819 | * | |
| Mark Skaletsky | 72,500 | * | |
| M. James Barrett, Ph.D. (15) | 21,907,500 | 20.8% | |
| Charles A. Blixt (16) | 8,455,342 | 7.9% | |
| G. Steven Burrill (17) | 5,875,471 | 5.6% | |
| Errol B. De Souza, Ph.D. (18) | 25,000 | * | |
| Elaine V. Jones, Ph.D. (19) | 14,146,226 | 13.5% | |
| John P. Richard (20) | 32,500 | * | |
| Alan G. Walton, Ph.D. (21) | 6,728,928 | 6.4% | |
| All executive officers and directors as a group (14 persons) (22) | 61,405,417 | 55.8% | |

* Indicates less than one percent.

- (1) Our calculation of the percentage of shares of common stock beneficially owned before this offering is based on 105,130,502 shares of our common stock and common stock equivalents outstanding as of December 31, 2004, assuming conversion of all outstanding shares of our series A, series B and series C convertible preferred stock. Our calculation of the percentage of shares beneficially owned after this offering is based on _____ shares of common stock to be outstanding after this offering, including the _____ shares that we are selling in this offering, our issuance of _____ shares of common stock upon conversion of an outstanding convertible promissory note concurrently with completion of this offering based on an assumed initial offering price of \$ _____ per share and our issuance of _____ shares of common stock upon the exercise of an outstanding warrant that will be cancelled if not exercised concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share.
- (2) Includes 21,851,340 shares owned of record by New Enterprise Associates 10, Limited Partnership, for which voting and investment power is shared by M. James Barrett, Stewart Alsop, Peter J. Barris, C. Richard Kramlich, Peter T. Morris, Charles W. Newhall, III, Mark W. Perry, Scott D. Sandell and Eugene A. Trainor, III, each of whom is a general partner of NEA Partners 10, Limited Partnership, the general partner of New Enterprise Associates 10, Limited Partnership; 23,660 shares owned of record by NEA Ventures 2002, Limited Partnership, for which voting and investment power is held by its general partner, Pamela J. Clark; and 32,500 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by NEA Development Corp., for which voting and investment power is shared by Charles W. Newhall, III, Mark W. Perry, Peter J. Barris, C. Richard Kramlich and Peter T. Morris as a result of their ownership of New Enterprise Associates, LLC. New Enterprise Associates, LLC is the sole owner of NEA Development Corp. Dr. Barrett, one of our directors, and each of the other general partners of NEA Partners 10, Limited Partnership disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his pecuniary interest therein.
- (3) Includes 11,320,512 shares owned of record by, and 40,000 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by, EuclidSR Partners, L.P., for which voting and investment power is shared by Elaine V. Jones, Graham D.S. Anderson, Barbara J. Dalton, A. Bliss McCrum, Milton J. Pappas, Stephen K. Reidy and Raymond J. Whitaker, each of whom are general partners of EuclidSR Associates, L.P., the general partner of EuclidSR Partners, L.P.; and 2,785,714 shares owned of record by EuclidSR Biotechnology Partners, L.P.,

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for which voting and investment power is shared by Elaine V. Jones, Graham D.S. Anderson, Barbara J. Dalton, A. Bliss McCrum, Milton J. Pappas, Stephen K. Reidy and Raymond J. Whitaker, each of whom are general partners of EuclidSR Biotechnology Associates, L.P., the general partner of EuclidSR Biotechnology Partners, L.P. Dr. Jones, one of our directors, and each of the other general partners of EuclidSR Associates, L.P. and EuclidSR Biotechnology Associates, L.P. disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his or her pecuniary interest therein.

- (4) Includes 8,928,571 shares owned of record by Nomura International plc and 7,098,214 shares owned of record by Nomura Phase4 Ventures LP. Nomura Phase4 Ventures Limited, as appointee of Nomura International plc and as manager of Nomura Phase4 Ventures LP, has voting and investment power over the shares held by Nomura International plc and Nomura Phase4 Ventures LP. Mr. Yoshiki Hashimoto, the Head of Merchant Banking, Nomura International plc, and Dr. Denise Pollard-Knight, the Head of Nomura Phase4 Ventures, are the only two members of the board of directors of Nomura Phase4 Ventures Limited and both of them, acting together, exercise the voting and investment power of Nomura Phase4 Ventures Limited. Mr. Hashimoto exercises these powers in his capacity as director of Nomura Phase4 Ventures Limited and as Head of Merchant Banking, Nomura International plc. Mr. Hashimoto and Dr. Pollard-Knight disclaim beneficial ownership of these shares.
- (5) Includes 6,629,907 shares owned of record by Oxford Bioscience Partners IV L.P. and 66,521 shares owned of record by mRNA Fund II L.P., for which voting and investment power is shared by Alan G. Walton, Jonathan J. Fleming, Jeffrey T. Barnes, Mark P. Carthy and Michael Lytton, each of whom are general partners of OBP Management IV L.P., the sole general partner of Oxford Bioscience Partners IV L.P. and mRNA Fund II L.P.; and 32,500 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by Oxford Bioscience IV Corporation, for which voting and investment power is shared by Alan G. Walton and Jonathan J. Fleming, each of whom are directors of Oxford Bioscience IV Corporation. Each of Oxford Bioscience Partners IV L.P. and mRNA Fund II L.P. disclaim beneficial ownership of any shares held of record by the other. Dr. Walton, one of our directors, and each of the other general partners of OBP Management IV L.P. disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his pecuniary interest therein.
- (6) Includes 31,725 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 and 1,612,903 shares issuable upon the exercise of an outstanding warrant, assuming that the warrant is exercised in full for cash. Voting and investment power is held by Andrew J. Schindler, the chief executive officer of R.J. Reynolds Tobacco Holdings, Inc. Mr. Blixt, one of our directors, is executive vice president, general counsel and assistant secretary of R.J. Reynolds Tobacco Holdings, Inc. and disclaims beneficial ownership of these shares.
- (7) Includes 5,835,471 shares owned of record by Burrill Biotechnology Capital Fund, L.P., for which voting and investment power is shared by G. Steven Burrill, John H. Kim, Roger E. Wyse, Michael K. Ullman and Ann F. Hanham, members of Burrill & Company (Biotechnology GP), LLC, the general partner of Burrill Biotechnology Capital Fund, L.P.; and 40,000 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by Burrill & Company LLC, for which voting and investment power is held by G. Steven Burrill, the chief executive officer of Burrill & Company LLC. Mr. Burrill, one of our directors, and each of the other members of Burrill & Company (Biotechnology GP), LLC disclaims beneficial ownership of the shares held by Burrill Biotechnology Capital Fund, L.P. except to the extent of his or her pecuniary interest therein.
- (8) Includes 1,955,138 shares owned of record by Advent Private Equity Fund II 'A' Limited Partnership; 1,192,418 shares owned of record by Advent Private Equity Fund II 'B' Limited Partnership; 1,775,200 shares owned of record by Advent Private Equity Fund II 'C' Limited Partnership; and 421,643 shares owned of record by Advent Private Equity Fund II 'D' Limited Partnership. Patrick Lee is a director of Advent Limited and a general partner of Advent Venture Partners LLP, which owns 100% of Advent Limited. Advent Limited owns 100% of Advent Management II Limited, which is the general partner of Advent Management II Limited Partnership, the general partner of each of the partnerships constituting Advent Private Equity Fund II. Voting and investment power over the shares held by each of the

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partnerships constituting Advent Private Equity Fund II is exercised by Advent Limited in its role as manager. The board of directors of Advent Limited consists of Sir David James Scott Cooksey (chairman), Peter Anthony Baines, Jerry Christopher Benjamin, David Cheesman, Leslie Ian Gabb, Patrick Pak-tin Lee, Martin Alexander McNair, James Anthony McNaught-Davis and Nicholas James Teasdale. Each director disclaims beneficial ownership of these shares except to the extent of his pecuniary interest therein.

- (9) Includes 1,029,003 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (10) Includes 559,848 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (11) Consists of 85,667 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (12) Includes 547,709 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (13) Includes 443,584 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (14) Includes 488,819 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (15) Includes 21,851,340 shares owned of record by New Enterprise Associates 10, Limited Partnership, for which voting and investment power is shared by M. James Barrett, Stewart Alsop, Peter J. Barris, C. Richard Kramlich, Peter T. Morris, Charles W. Newhall, III, Mark W. Perry, Scott D. Sandell and Eugene A. Trainor, III, each of whom is a general partner of NEA Partners 10, Limited Partnership, the general partner of New Enterprise Associates 10, Limited Partnership; 23,660 shares owned of record by NEA Ventures 2002, Limited Partnership, for which voting and investment power is held by its general partner, Pamela J. Clark; and 32,500 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by NEA Development Corp., for which voting and investment power is shared by Charles W. Newhall, III, Mark W. Perry, Peter J. Barris, C. Richard Kramlich and Peter T. Morris through their ownership of New Enterprise Associates, LLC. New Enterprise Associates, LLC is the sole owner of NEA Development Corp. Dr. Barrett, one of our directors, and each of the other general partners of NEA Partners 10, Limited Partnership disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his pecuniary interest therein.
- (16) Includes 31,725 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 and 1,612,903 shares issuable upon the exercise of an outstanding warrant, assuming that the warrant is exercised in full for cash. Voting and investment power is held by Andrew J. Schindler, the chief executive officer of R.J. Reynolds Tobacco Holdings, Inc. Mr. Blixt is executive vice president, general counsel and assistant secretary of R.J. Reynolds Tobacco Holdings, Inc. and disclaims beneficial ownership of these shares.
- (17) Includes 5,835,471 shares owned of record by Burrill Biotechnology Capital Fund, L.P., for which voting and investment power is shared by G. Steven Burrill, John H. Kim, Roger E. Wyse, Michael K. Ullman and Ann F. Hanham, members of Burrill & Company (Biotechnology GP), LLC, the general partner of Burrill Biotechnology Capital Fund, L.P.; and 40,000 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by Burrill & Company LLC, for which voting and investment power is held by G. Steven Burrill, the chief executive officer of Burrill & Company LLC. Mr. Burrill, one of our directors, and each of the other members of Burrill & Company (Biotechnology GP), LLC disclaims beneficial ownership of the shares held by Burrill Biotechnology Capital Fund, L.P. except to the extent of his or her pecuniary interest therein.
- (18) Issuable upon exercise of stock options exercisable within sixty days of December 31, 2004.
- (19) Includes 11,320,512 shares owned of record by, and 40,000 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by, EuclidSR Partners, L.P., for which voting and investment power is shared by Elaine V. Jones, Graham D.S. Anderson, Barbara J. Dalton, A. Bliss McCrum, Milton J. Pappas, Stephen K. Reidy and Raymond J.

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Whitaker, each of whom are general partners of EuclidSR Associates, L.P., the general partner of EuclidSR Partners, L.P.; and 2,785,714 shares owned of record by EuclidSR Biotechnology Partners, L.P., for which voting and investment power is shared by Elaine V. Jones, Graham D.S. Anderson, Barbara J. Dalton, A. Bliss McCrum, Milton J. Pappas, Stephen K. Reidy and Raymond J. Whitaker, each of whom are general partners of EuclidSR Biotechnology Associates, L.P., the general partner of EuclidSR Biotechnology Partners, L.P. Dr. Jones, one of our directors, and each of the other general partners of EuclidSR Associates, L.P. and EuclidSR Biotechnology Associates, L.P. disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his or her pecuniary interest therein.

- (20) Includes 7,500 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004.
- (21) Includes 6,629,907 shares owned of record by Oxford Bioscience Partners IV L.P. and 66,521 shares owned of record by mRNA Fund II L.P., for which voting and investment power is shared by Alan G. Walton, Jonathan J. Fleming, Jeffrey T. Barnes, Mark P. Carthy and Michael Lytton, each of whom are general partners of OBP Management IV L.P., the sole general partner of Oxford Bioscience Partners IV L.P. and mRNA Fund II L.P.; and 32,500 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 held by Oxford Bioscience IV Corporation, for which voting and investment power is shared by Alan G. Walton and Jonathan J. Fleming, each of whom are directors of Oxford Bioscience IV Corporation. Dr. Walton and each of the other general partners of OBP Management IV L.P. disclaims beneficial ownership of the shares held by each of the aforementioned entities except to the extent of his pecuniary interest therein.
- (22) Includes 3,363,855 shares of common stock issuable upon exercise of stock options exercisable within 60 days of December 31, 2004 and 1,612,903 shares issuable upon the exercise of an outstanding warrant, assuming that the warrant is exercised in full for cash.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our certificate of incorporation and bylaws are summaries and are qualified by reference to the certificate of incorporation and the bylaws that will be in effect upon completion of this offering. Copies of these documents have been filed with the Securities and Exchange Commission as exhibits to our registration statement of which this prospectus forms a part. The descriptions of the common stock and preferred stock reflect changes to our capital structure that will occur concurrently with the completion of this offering.

Upon completion of this offering, our authorized capital stock will consist of _____ shares of common stock, par value \$0.001 per share, and _____ shares of undesignated preferred stock, par value \$0.001 per share.

As of December 31, 2004, we had outstanding:

- 1,926,313 shares of common stock held by 55 stockholders of record;
- 5,000,000 shares of series A convertible preferred stock;
- 6,567,567 shares of series B convertible preferred stock; and
- 76,441,866 shares of series C convertible preferred stock.

As of December 31, 2004, we also had outstanding a convertible promissory note in the original principal amount of \$1.25 million that will convert into _____ shares of common stock based on the price per share in this offering and a warrant to purchase 1,612,903 shares of common stock at an exercise price of \$1.95 per share.

All of our outstanding shares of preferred stock will convert into 103,204,189 shares of common stock concurrently with the completion of this offering. In addition, the convertible promissory note will convert into _____ shares of common stock concurrently with completion of this offering based on an assumed initial public offering price of \$ _____ per share. Also, the warrant will be cancelled if it is not exercised prior to the completion of this offering. If R.J. Reynolds exercises the warrant in full for cash, we would issue 1,612,903 shares of common stock and receive cash proceeds of approximately \$3.1 million. If R.J. Reynolds exercises the warrant on a cashless basis, we would issue _____ shares of common stock, based on an assumed initial public offering price of \$ _____ per share.

Common Stock

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors, and there are no cumulative voting rights. Subject to preferences that may be applicable to any shares of preferred stock that may become outstanding from time to time, holders of common stock are entitled to receive, ratably, dividends declared from time to time by our board of directors, if any, out of funds legally available for that purpose. In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any shares of preferred stock then outstanding. Holders of common stock have no conversion, preemptive or other subscription rights, and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock

Upon completion of this offering, our board of directors will be authorized, without stockholder approval, to issue up to an aggregate of _____ shares of preferred stock in one or more series and to fix the rights, preferences, designation and powers granted to or imposed upon the preferred stock, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences. We cannot state with

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certainly the actual effects of the issuance of any shares of preferred stock upon the rights of holders of common stock until the board of directors determines the specific rights of the holders of the preferred stock. Some of these effects might potentially include:

- restricting the declaration or payment of dividends on the common stock;
- diluting the voting power of the common stock;
- impairing the liquidation rights of the common stock; and
- delaying or preventing a change in control of us.

We do not currently have any plans to issue any shares of preferred stock following this offering.

Options

As of December 31, 2004, options to purchase 7,408,736 shares of common stock at a weighted average exercise price of \$0.65 per share were outstanding.

Registration Rights

After this offering, holders of approximately _____ shares of our common stock will have the right to require us to register the sales of their shares under the Securities Act, under the terms of an agreement between us and the holders of these securities. Subject to limitations specified in this agreement, these registration rights include the following:

Demand Registration Rights. Beginning six months after the completion of this offering, subject to specified limitations, two separate constituencies of the holders of registrable securities may require that we register part of these securities for sale under the Securities Act. Each constituency may make one such demand.

Incidental Registration Rights. If we register any of our common stock under the Securities Act, solely for cash, either for our own account or for the account of other security holders, the holders of shares of registrable securities are entitled to notice of the registration and to include their shares of common stock in the registration. These rights have been waived for this offering.

Form S-3 Registration Rights. If we become eligible to file registration statements on Form S-3, holders of registrable securities can require us to register their registrable securities on Form S-3 if the total gross proceeds to be received by them together would be at least \$1.0 million.

Limitations and Expenses. With specified exceptions, a holder's right to include shares in a registration statement is subject to the right of the underwriters to limit the number of shares included in the offering. We are generally required to pay all expenses of registration, including the fees and expenses of one legal counsel to the registering security holders up to a prescribed maximum amount, but excluding underwriters' discounts and commissions.

Anti-Takeover Provisions

We are subject to Section 203 of the Delaware General Corporation Law, an anti-takeover statute. Subject to certain exceptions, Section 203 prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A business combination includes, among other things, a merger or consolidation involving us and the interested stockholder and the sale of more than 10% of our assets. In general, an interested stockholder is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by that entity or person.

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Certain provisions of our certificate of incorporation and bylaws that will be in effect upon completion of this offering could make the acquisition of us through a tender offer, proxy contest or other means, or the removal of incumbent officers and directors, more difficult. These provisions may discourage certain types of coercive takeover practices and takeover bids and encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of retaining the ability to negotiate with a proponent of an unfriendly or unsolicited proposal outweigh the potential disadvantages of discouraging such a proposal. These provisions may make it more difficult for stockholders to take specific corporate actions and could have the effect of delaying or preventing a change in our control.

In particular, our certificate of incorporation or bylaws provide for the following:

Staggered Board of Directors and Number of Directors. Our board of directors is divided into three classes of the same or nearly the same number of directors serving staggered three-year terms, which means that only one class of directors may be elected at a particular stockholders meeting. Also, the authorized number of directors comprising our board of directors may only be changed by resolution of our board of directors. As a result, the replacement of incumbent directors may be more difficult and third parties may be discouraged from seeking to circumvent the anti-takeover provisions of our certificate of incorporation and bylaws by replacing our incumbent directors.

Limitations on Calling Special Meetings of Stockholders. Under Delaware law, a special meeting of stockholders may be called by the board of directors or by any other person authorized to do so in the certificate of incorporation or the bylaws. Our certificate of incorporation and bylaws do not permit our stockholders to call a special meeting. As a result, a stockholder could not force stockholder consideration of a proposal over the opposition of the board of directors by calling a special meeting. The restriction on the ability of stockholders to call a special meeting means that a proposal to replace the board of directors also could be delayed until the next annual meeting.

Advance Notice Procedures. Our bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to the board of directors. At an annual meeting, stockholders may consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of the board of directors. Stockholders may also consider a proposal or nomination by a person who was a stockholder of record on the record date for the meeting and on the date that notice of the proposal or nomination was given, who is entitled to vote at the meeting and who has given to our secretary timely written notice, in proper form, of his or her intention to bring that business before the meeting. The bylaws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of us.

Prohibition of Stockholder Action by Written Consent. Delaware law provides that, unless prohibited by the certificate of incorporation, stockholders may execute an action by written consent in lieu of a stockholder meeting. Our certificate of incorporation prohibits stockholder action by written consent, which may lengthen the amount of time required to take stockholder actions because actions by written consent are not subject to the minimum notice requirement of a stockholders meeting. The prohibition of stockholder action by written consent may deter hostile takeover attempts because a holder that controlled a majority of our capital stock would not be able to amend our bylaws or remove directors without holding a stockholders meeting and would have to obtain the consent of a majority of our board of directors, our chairman of the board, our chief executive officer or our president to call a stockholders meeting and satisfy the applicable notice periods.

Undesignated Preferred Stock. Our board of directors is authorized to issue up to _____ shares of our preferred stock in one or more series and to fix the rights, preferences, designation and powers granted to or imposed upon the preferred stock, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences. The existence of this ability could discourage an attempt to take control of us through a merger, tender offer, proxy contest or other means.

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With the exception of the provision relating to the issuance of preferred stock, which can be amended with the approval of a majority of the outstanding shares of stock entitled to vote, none of these provisions can be amended without the approval of at least two-thirds of our outstanding shares of stock entitled to vote. In addition, the affirmative vote of two-thirds of our outstanding shares of stock entitled to vote is required to amend provisions of our certificate of incorporation or bylaws relating to exculpation and indemnification of directors and officers, the number, election, qualification, term of office, resignation or removal of directors and the filling of director vacancies.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

NASDAQ National Market

We have applied to have our common stock listed on the NASDAQ National Market under the symbol "TRGT."

SHARES ELIGIBLE FOR FUTURE SALE

Prior to this offering, there has been no public market for our common stock and we cannot assure you that a liquid trading market for our common stock will develop or be sustained after this offering. Future sales of substantial amounts of our common stock in the public market following this offering, or the anticipation of those sales, could adversely affect market prices prevailing from time to time and could impair our ability to raise capital by the sale of our equity securities.

Upon completion of this offering, we will have outstanding _____ shares of common stock, after giving effect to the conversion of all outstanding shares of our convertible preferred stock into 103,204,189 shares of common stock concurrently with the completion of this offering, our issuance of _____ shares of common stock upon conversion of an outstanding convertible promissory note concurrently with the completion of this offering based on an assumed initial public offering price of \$ _____ per share and our issuance of _____ shares of common stock upon the exercise of an outstanding warrant that will be cancelled if not exercised concurrently with the completion of this offering, assuming that the warrant is exercised on a cashless basis based on an assumed initial public offering price of \$ _____ per share. If the warrant is exercised in full for cash, we would issue 1,612,903 shares of our common stock.

All of the _____ shares sold in this offering will be freely tradable without restriction unless purchased by our “affiliates,” as that term is defined in Rule 144 under the Securities Act. The remaining _____ shares of common stock to be outstanding after this offering are “restricted securities” under Rule 144. All of these restricted securities will be subject to the 180-day lock-up period described below. Immediately after the 180-day lock-up period, _____ shares will be freely tradable under Rule 144(k) or Rule 701(c)(3) under the Securities Act and _____ shares will be eligible for resale under Rule 144, subject to volume limitations.

Restricted securities may be sold in the public market only if registered or if they qualify for an exemption from registration under Rules 144 or 701 under the Securities Act. These rules are summarized below.

Rule 144

In general, under Rule 144, beginning 90 days after the date of this prospectus, a person who has beneficially owned shares of our common stock for at least one year would be entitled to sell within any three-month period a number of shares that does not exceed the greater of:

- 1% of the number of shares of common stock then outstanding, which will equal approximately _____ shares immediately after this offering; or
- the average weekly trading volume of the common stock on the NASDAQ National Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to the sale.

Sales under Rule 144 are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

Rule 144(k)

Subject to the lock-up agreements described below, shares of our common stock eligible for sale under Rule 144(k) may be sold immediately after the completion of this offering. In general, under Rule 144(k), a person may sell shares of common stock acquired from us immediately after the completion of this offering, without regard to manner of sale, notice, availability of public information or volume, if:

- the person is not our affiliate and has not been our affiliate at any time during the three months preceding the sale; and
- the person has beneficially owned the shares proposed to be sold for at least two years, including the holding period of any prior owner other than an affiliate.

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Rule 701

In general, under Rule 701, any of our employees, consultants or advisors who purchased shares from us in connection with a qualified compensatory benefit plan or other written compensation contract is eligible to resell those shares 90 days after the effective date of this offering in reliance on Rule 144, but without compliance with various restrictions, including the holding period, contained in Rule 144.

Lock-up Agreements

The holders of substantially all of our currently outstanding stock have agreed that, without the prior written consent of Deutsche Bank Securities Inc. on behalf of the underwriters and subject to the exceptions described in the section entitled “Underwriters” in this prospectus they will not, during the period ending 180 days after the date of this prospectus, subject to a possible extension:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for shares of our common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of shares of our common stock,

whether any transaction described above is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise. Deutsche Bank Securities does not have any pre-established conditions to waiving the terms of the lock-up agreements. Any determination to release any shares subject to the lock-up agreements would be based on a number of factors at the time of determination, including but not necessarily limited to the market price of the common stock, the liquidity of the trading market for the common stock, general market conditions, the number of shares proposed to be sold and the timing, purpose and terms of the proposed sale.

The lock-up agreements also provide that, if we issue an earnings release or if material news or a material event relating to our company occurs during the last 17 days of the 180-day restricted period or if prior to the expiration of the 180-day restricted period we announce that we will release earnings results during the 16-day period beginning on the last day of the 180-day period, the restricted period will continue for the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

Stock Options

After the completion of this offering, we intend to file a registration statement on Form S-8 under the Securities Act to register all of the shares of common stock subject to issuance upon exercise of outstanding options granted under, or reserved for future issuance under, our 2000 plan and our 2005 plan. Shares of common stock issued under the Form S-8 upon exercise of options will be available for sale in the public market, subject to Rule 144 volume limitations applicable to affiliates and subject to the contractual restrictions described above. As of December 31, 2004, options to purchase 7,408,736 shares of common stock were outstanding under our 2000 plan with a weighted average exercise price of \$0.65, of which approximately 4,400,303 were vested and exercisable with a weighted average exercise price of \$0.62 and an additional 302,143 shares were reserved for issuance under our 2000 plan. Upon completion of this offering, those shares reserved under our 2000 plan plus an additional _____ shares of common stock will become reserved for issuance under our 2005 plan.

Registration Rights

Upon completion of this offering, the holders of _____ shares of our common stock will be entitled to registration rights. Registration of the sale of these shares upon exercise of these rights would make them freely tradable without restriction under the Securities Act. For more information regarding these registration rights, see “Description of Capital Stock—Registration Rights.”

UNDERWRITERS

Under the terms and subject to the conditions contained in an underwriting agreement dated the date of this prospectus, the underwriters named below, for whom Deutsche Bank Securities Inc., Pacific Growth Equities, LLC, CIBC World Markets Corp. and Lazard Frères & Co. LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

| Name | Number of Shares |
|-------------------------------|---------------------|
| Deutsche Bank Securities Inc. | |
| Pacific Growth Equities, LLC | |
| CIBC World Markets Corp. | |
| Lazard Frères & Co. LLC | |
| <hr/> | |
| Total | |

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of specified legal matters by their counsel and to other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the public offering price listed on the cover page of this prospectus and part to certain dealers at a price that represents a concession not in excess of \$ _____ per share under the public offering price. No underwriter may allow, and no dealer may reallocate, any concession to other underwriters or to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to an aggregate of _____ additional shares of common stock at the public offering price listed on the cover page of this prospectus, less underwriting discounts and commissions. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase approximately the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table. If the underwriters' option is exercised in full, the total price to the public would be \$ _____, the total underwriters' discounts and commissions would be \$ _____ and the total proceeds to us would be \$ _____.

The underwriters have informed us that they do not intend sales to discretionary accounts to exceed five percent of the total number of shares of common stock offered by them.

We and all of our directors and officers and holders of substantially all of our outstanding stock have agreed that, without the prior written consent of Deutsche Bank Securities on behalf of the underwriters, we and they will not, during the period ending 180 days after the date of this prospectus:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for shares of our common stock; or

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- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of shares of our common stock,

whether any transaction described above is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise.

The 180-day restricted period described in the preceding paragraph will be extended if:

- during the last 17 days of the 180-day restricted period we issue an earnings release or material news or a material event relating to our company occurs; or
- prior to the expiration of the 180-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 180-day period,

in which case the restrictions described in the preceding paragraph will continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

These restrictions do not apply to:

- the sale of shares to the underwriters;
- the issuance by us of shares of our common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus of which the underwriters have been advised in writing;
- the issuance by us of shares or options to purchase shares of our common stock pursuant to our 2000 plan or our 2005 plan, provided that the recipient of the shares agrees to be subject to the restrictions described above;
- transactions by any person other than us relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares;
- transfers of shares as a gift or charitable contribution, or by will or intestacy;
- transfers of shares to any trust the sole beneficiaries of which are the transferee or a member of the immediate family of the transferee; or
- transfers to certain entities or persons affiliated with the stockholder;

provided that in the case of each of the last three transactions, each donee, distributee, transferee and recipient agrees to be subject to the restrictions described in the immediately preceding paragraph, no filing under Section 16 of the Securities Exchange Act of 1934, as amended, is required in connection with these transactions, other than a filing on a Form 5 made after the expiration of the 180-day period, and no transaction includes a disposition for value.

The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares of our common stock.

| | Paid by Targacept | |
|-----------|-------------------|---------------|
| | No Exercise | Full Exercise |
| Per share | \$ | \$ |
| Total | \$ | \$ |

In addition, we estimate that the expenses of this offering payable by us, other than underwriting discounts and commissions, will be \$.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell

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more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. In addition, to stabilize the price of the common stock, the underwriters may bid for, and purchase, shares of common stock in the open market. Finally, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the common stock in this offering, if the syndicate repurchases previously distributed common stock in transactions to cover syndicate short positions or to stabilize the price of the common stock. Any of these activities may stabilize or maintain the market price of the common stock above independent market levels. The underwriters are not required to engage in these activities, and may end any of these activities at any time.

We have applied for quotation of our common stock on the NASDAQ National Market under the symbol “TRGT.”

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

Directed Share Program

At our request, the underwriters have reserved for sale, at the initial public offering price, up to _____ shares offered by this prospectus to directors, officers, employees and other individuals associated with us and members of their respective families and friends through a directed share program. The number of shares of our common stock available for sale to the general public in the offering will be reduced to the extent these persons purchase these reserved shares. Any reserved shares not purchased by these persons will be offered by the underwriters to the general public on the same basis as the other shares offered by this prospectus. Recipients of reserved shares will be required to agree with the underwriters not to sell, transfer, assign, pledge or hypothecate these shares for a period of 180 days after purchasing the shares.

Pricing of the Offering

Prior to the offering, there has been no public market for our common stock. The initial public offering price will be determined by negotiations between us and the representatives. Among the factors to be considered in determining the initial public offering price of the shares will be our future prospects and those of our industry in general, our sales, earnings and other financial operating information in recent periods, and the price-earnings ratios, price-sales ratios, market prices of securities and financial and operating information of companies engaged in activities similar to ours. The estimated initial public offering price range set forth on the cover page of this preliminary prospectus is subject to change as a result of market conditions and other factors.

LEGAL MATTERS

Certain legal matters with respect to the validity of the shares of common stock offered hereby will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts and by Womble Carlyle Sandridge & Rice, PLLC, Winston-Salem, North Carolina. Wilmer Cutler Pickering Hale and Dorr LLP, New York, New York, has acted as counsel for the underwriters in connection with certain legal matters related to this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, have audited our financial statements as of December 31, 2003 and 2002 and for each of the three years in the period ended December 31, 2003, as set forth in their report. We have included our financial statements in the prospectus and elsewhere in the registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the Securities and Exchange Commission a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock to be sold in this offering. This prospectus does not contain all of the information set forth in the registration statement. You should refer to the registration statement for additional information regarding us and the shares of our common stock to be sold in this offering. Whenever we reference any contract, agreement or other document in this prospectus, the reference is not necessarily complete and you should refer to the exhibits to the registration statement for the actual contract, agreement or other document. In each instance, reference is made to such exhibits and each such statement is qualified in all respects by such reference. In addition, when this offering is completed, we will become subject to the information and reporting requirements of the Exchange Act and, in accordance with the Exchange Act, will file periodic reports, proxy statements and other information with the Securities and Exchange Commission.

You can read the registration statement and our future filings with the Securities and Exchange Commission over the Internet at the Securities and Exchange Commission's website at <http://www.sec.gov>. You may also read and copy any document that we file with the Securities and Exchange Commission at its public reference room at 450 Fifth Street, N.W., Washington, D.C. 20549.

You may obtain copies of the documents at prescribed rates by writing to the Public Reference Section of the Securities and Exchange Commission at 450 Fifth Street, N.W., Washington, D.C. 20549. Please call the Securities and Exchange Commission at 1-800-SEC-0330 for further information on the operation of the public reference room. Upon approval of our common stock for listing on the NASDAQ National Market, such reports, proxy and information statements and other information may also be inspected at the offices of NASDAQ Operations, 1735 K Street, N.W., Washington, D.C. 20006.

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Report of Independent Registered Public Accounting Firm

The Board of Directors
Targacept, Inc.

We have audited the accompanying balance sheets of Targacept, Inc. as of December 31, 2002 and 2003, and the related statements of operations, redeemable convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2003. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Targacept, Inc. at December 31, 2002 and 2003, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2003, in conformity with U.S. generally accepted accounting principles.

ERNST & YOUNG LLP

January 22, 2004, except for Note 18,
as to which the date is , 2005
Greensboro, North Carolina

The foregoing report is in the form that will be signed upon the completion of the restatement of capital accounts described in Note 18 to the financial statements.

/s/ ERNST & YOUNG LLP

January 20, 2005
Greensboro, North Carolina

Targacept, Inc.
Balance Sheets

| | December 31, | | September 30, | Pro forma Stockholders' equity as of September 30, 2004 |
|--|----------------------|----------------------|----------------------|--|
| | 2002 | 2003 | 2004 | |
| | | | (unaudited) | |
| Assets | | | | |
| Current assets: | | | | |
| Cash and cash equivalents | \$ 44,353,320 | \$ 11,609,157 | \$ 24,425,286 | |
| Short-term investments | 5,008,139 | 31,367,500 | — | |
| Research fees and accounts receivable | 1,335,648 | 818,618 | 205,328 | |
| Inventories | 169,536 | 118,520 | 106,275 | |
| Prepaid expenses | 423,016 | 514,552 | 1,521,330 | |
| Total current assets | 51,289,659 | 44,428,347 | 26,258,219 | |
| Property and equipment, net | 2,462,944 | 2,373,035 | 2,389,452 | |
| Intangible assets, net of accumulated amortization of \$15,735, \$53,499 and \$81,822 at December 31, 2002, 2003 and September 30, 2004, respectively | 626,265 | 588,501 | 560,178 | |
| Total assets | \$ 54,378,868 | \$ 47,389,883 | \$ 29,207,849 | |
| Liabilities, redeemable convertible preferred stock and stockholders' equity (deficit) | | | | |
| Current liabilities: | | | | |
| Accounts payable | \$ 1,503,170 | \$ 1,246,975 | \$ 1,873,536 | |
| Accrued expenses | 1,477,034 | 1,406,778 | 1,759,279 | |
| Current portion of long-term debt | 586,816 | 576,072 | 898,907 | |
| Current portion of deferred rent incentive | 402,647 | 402,647 | 402,647 | |
| Current portion of deferred license fee revenue | 634,881 | 269,537 | 269,537 | |
| Total current liabilities | 4,604,548 | 3,902,009 | 5,203,906 | |
| Long-term debt, net of current portion | 2,088,293 | 1,461,554 | 1,654,113 | |
| Deferred rent incentive, net of current portion | 1,442,818 | 1,040,171 | 738,185 | |
| Deferred license fee revenue, net of current portion | 1,551,875 | 1,647,687 | 1,445,534 | |
| Total liabilities | 9,687,534 | 8,051,421 | 9,041,738 | |
| Commitments | | | | |
| Redeemable convertible preferred stock: | | | | |
| Series A, \$0.001 par value, 5,000,000 shares authorized, issued and outstanding, aggregate liquidation preference of \$26,826,253, \$28,496,497 and \$29,749,180 at December 31, 2002, 2003, and September 30, 2004, respectively, or \$4.65 per share plus accreted redemption value | 26,826,253 | 28,496,497 | 29,749,180 | |
| Series B, \$0.001 par value, 6,567,567 shares authorized, issued and outstanding, aggregate liquidation preference of \$35,346,675, \$37,484,419 and \$39,087,725 at December 31, 2002, 2003, and September 30, 2004, respectively, or \$4.65 per share, plus accreted redemption value | 35,346,675 | 37,484,419 | 39,087,725 | |
| Series C, \$0.001 par value, 37,764,180, 49,169,138 and 49,169,138 shares authorized, issued and outstanding at December 31, 2002, 2003, and September 30, 2004, respectively, aggregate liquidation preference of \$45,853,329, \$64,153,421 and \$67,723,100 at December 31, 2002, 2003, and September 30, 2004, or \$1.21 per share, plus accreted redemption value | 45,853,329 | 64,153,421 | 67,723,100 | |
| Total redeemable convertible preferred stock | 108,026,257 | 130,134,337 | 136,560,005 | |
| Stockholders' equity (deficit): | | | | |
| Common stock, \$0.001 par value, 75,000,000, 85,000,000 and 85,000,000 shares authorized at December 31, 2002, 2003, and September 30, 2004, respectively, 624,584, 1,082,771 and 1,887,356 shares issued and outstanding at December 31, 2002, 2003, and September 30, 2004, respectively. | 625 | 1,083 | 1,888 | \$ |
| Capital in excess of par value | 386,854 | 690,675 | 1,225,177 | |
| Common stock warrants | 213,710 | 213,710 | 213,710 | |
| Accumulated deficit | (63,936,112) | (91,672,061) | (117,834,669) | |
| Accumulated other comprehensive loss | — | (29,282) | — | |
| Total stockholders' equity (deficit) | (63,334,923) | (90,795,875) | (116,393,894) | |
| Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit) | \$ 54,378,868 | \$ 47,389,883 | \$ 29,207,849 | \$ |

See accompanying notes.

Targacept, Inc.
Statements of Operations

| | Year ended December 31, | | | Nine months ended September 30, | |
|--|-------------------------|------------------------|------------------------|---------------------------------|------------------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| | | | | (unaudited) | |
| Revenue: | | | | | |
| Research fee revenue | \$ 1,100,000 | \$ 1,388,824 | \$ 1,302,500 | \$ 965,000 | \$ 208,806 |
| License fee revenue | 602,807 | 634,881 | 269,532 | 202,149 | 202,153 |
| Product sales | — | 242,861 | 814,724 | 582,365 | 584,167 |
| Other | 687 | 19,792 | 71,529 | 66,639 | 585,422 |
| Net revenue | 1,703,494 | 2,286,358 | 2,458,285 | 1,816,153 | 1,580,548 |
| Operating expenses: | | | | | |
| Research and development | 8,151,785 | 16,243,888 | 18,179,542 | 13,376,468 | 17,782,199 |
| General and administrative | 2,302,161 | 4,135,262 | 3,599,673 | 2,698,385 | 3,763,700 |
| Cost of product sales | — | 243,718 | 742,941 | 539,736 | 27,629 |
| Purchased in-process research and development | — | 2,666,000 | — | — | — |
| Total operating expenses | 10,453,946 | 23,288,868 | 22,522,156 | 16,614,589 | 21,573,528 |
| Loss from operations | (8,750,452) | (21,002,510) | (20,063,871) | (14,798,436) | (19,992,980) |
| Other income (expense): | | | | | |
| Interest and dividend income | 1,448,182 | 87,691 | 791,339 | 546,263 | 355,638 |
| Interest expense | — | (102,891) | (122,789) | (95,753) | (95,755) |
| Loss on disposal of fixed assets | — | (53,996) | — | — | (3,843) |
| Total other income (expense) | 1,448,182 | (69,196) | 668,550 | 450,510 | 256,040 |
| Net loss | (7,302,270) | (21,071,706) | (19,395,321) | (14,347,926) | (19,736,940) |
| Preferred stock accretion | (3,807,988) | (4,173,545) | (8,340,628) | (6,198,736) | (6,425,668) |
| Net loss attributable to common stockholders | \$ (11,110,258) | \$ (25,245,251) | \$ (27,735,949) | \$ (20,546,662) | \$ (26,162,608) |
| Basic and diluted net loss attributable to common stockholders per share | \$ (26.80) | \$ (45.28) | \$ (33.91) | \$ (27.04) | \$ (16.82) |
| Weighted average common shares outstanding—basic and diluted | 414,624 | 557,492 | 817,894 | 759,937 | 1,555,090 |
| Pro forma basic and diluted net loss per share attributable to common stockholders assuming conversion of preferred stock (unaudited) | | | \$ (0.27) | | \$ (0.26) |
| Pro forma weighted average shares outstanding—basic and diluted (unaudited) | | | 71,118,629 | | 75,294,995 |

See accompanying notes.

Targacept, Inc.
Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

| | Redeemable Convertible Preferred Stock | | | Common Stock | | Capital in Excess of Par Value | Common Stock Warrants | Deferred Compensation | Accumulated Deficit | Accumulated Other Comprehensive Loss | Total Stockholders' Deficit |
|--|--|---------------------|---------------------|----------------|---------------|--------------------------------|-----------------------|-----------------------|------------------------|--------------------------------------|-----------------------------|
| | Series A | Series B | Series C | Shares | Amount | | | | | | |
| Balances at December 31, 2000 | \$23,485,765 | \$30,932,000 | \$ — | 309,424 | \$ 309 | \$145,120 | \$ 213,710 | \$ (92,638) | \$ (27,580,603) | \$ — | \$ (27,314,102) |
| Stock issuance costs | — | — | — | — | — | (42,496) | — | — | — | — | (42,496) |
| Issuance of 29,933 shares of Series B redeemable convertible preferred stock at \$4.65 per share | — | 139,188 | — | — | — | — | — | — | — | — | — |
| Issuance of 111,111 shares of common stock valued at \$0.68 per share, related to collaborative research and development agreement | — | — | — | 111,111 | 111 | 75,445 | — | — | — | — | 75,556 |
| Issuance of 65,565 shares of common stock at \$0.001 per share par value, related to exercise of stock options | — | — | — | 65,565 | 66 | 30,749 | — | — | — | — | 30,815 |
| Accreted redemption value for common stock warrants attached to Series A redeemable convertible preferred stock | 42,744 | — | — | — | — | — | — | — | (42,744) | — | (42,744) |
| Accreted redemption value for Series A and Series B redeemable convertible preferred stock | 1,627,500 | 2,137,744 | — | — | — | — | — | — | (3,765,244) | — | (3,765,244) |
| Amortization of deferred compensation | — | — | — | — | — | — | — | 92,638 | — | — | 92,638 |
| Net loss | — | — | — | — | — | — | — | — | (7,302,270) | — | (7,302,270) |
| Balances at December 31, 2001 | 25,156,009 | 33,208,932 | — | 486,100 | 486 | 208,818 | 213,710 | — | (38,690,861) | — | (38,267,847) |
| Stock issuance costs | — | — | (206,887) | — | — | — | — | — | — | — | — |
| Issuance of 37,764,180 shares of Series C redeemable convertible preferred stock at \$1.21 per share | — | — | 45,694,658 | — | — | — | — | — | — | — | — |
| Issuance of 138,484 shares of common stock at \$0.001 per share par value, related to exercise of stock options | — | — | — | 138,484 | 139 | 178,036 | — | — | — | — | 178,175 |
| Accreted redemption value for common stock warrants attached to Series A redeemable convertible preferred stock | 42,744 | — | — | — | — | — | — | — | (42,744) | — | (42,744) |
| Accreted redemption value for Series A, Series B, and Series C redeemable convertible preferred stock | 1,627,500 | 2,137,743 | 365,558 | — | — | — | — | — | (4,130,801) | — | (4,130,801) |
| Net loss | — | — | — | — | — | — | — | — | (21,071,706) | — | (21,071,706) |
| Balances at December 31, 2002 | \$26,826,253 | \$35,346,675 | \$45,853,329 | 624,584 | \$ 625 | \$386,854 | \$ 213,710 | \$ — | \$ (63,936,112) | \$ — | \$ (63,334,923) |

Targacept, Inc.
Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)—(continued)

| | Redeemable Convertible Preferred Stock | | | Common Stock | | Capital in Excess of Par Value | Common Stock Warrants | Deferred Compensation | Accumulated Deficit | Accumulated Other Comprehensive Loss | Total Stockholders' Deficit |
|---|--|--------------|--------------|--------------|----------|--------------------------------|-----------------------|-----------------------|---------------------|--------------------------------------|-----------------------------|
| | Series A | Series B | Series C | Shares | Amount | | | | | | |
| Balances at December 31, 2002 (carried forward) | \$26,826,253 | \$35,346,675 | \$45,853,329 | 624,584 | \$ 625 | \$ 386,854 | \$ 213,710 | \$ — | \$ (63,936,112) | \$ — | \$ (63,334,923) |
| Stock issuance costs | — | — | (32,548) | — | — | — | — | — | — | — | — |
| Issuance of 11,404,958 shares of Series C redeemable convertible preferred stock at \$1.21 per share | — | — | 13,800,000 | — | — | — | — | — | — | — | — |
| Issuance of 458,187 shares of common stock at \$0.001 per share par value, related to exercise of stock options | — | — | — | 458,187 | 458 | 303,821 | — | — | — | — | 304,279 |
| Accreted redemption value for common stock warrants attached to Series A redeemable convertible preferred stock | 42,744 | — | — | — | — | — | — | — | (42,744) | — | (42,744) |
| Accreted redemption value for Series A, Series B, and Series C redeemable convertible preferred stock | 1,627,500 | 2,137,744 | 4,532,640 | — | — | — | — | — | (8,297,884) | — | (8,297,884) |
| Net change in unrealized holding loss on available-for-sale securities | — | — | — | — | — | — | — | — | — | (29,282) | (29,282) |
| Net loss | — | — | — | — | — | — | — | — | (19,395,321) | — | (19,395,321) |
| Comprehensive loss | — | — | — | — | — | — | — | — | — | — | (19,424,603) |
| Balances at December 31, 2003 | 28,496,497 | 37,484,419 | 64,153,421 | 1,082,771 | 1,083 | 690,675 | 213,710 | — | (91,672,061) | (29,282) | (90,795,875) |
| Issuance of 804,585 shares of common stock at \$0.001 per share par value, related to exercise of stock options (unaudited) | — | — | — | 804,585 | 805 | 534,502 | — | — | — | — | 535,307 |
| Accreted redemption value for common stock warrants attached to Series A redeemable convertible preferred stock (unaudited) | 32,058 | — | — | — | — | — | — | — | (32,058) | — | (32,058) |
| Accreted redemption value for Series A Series B and Series C redeemable convertible preferred stock (unaudited) | 1,220,625 | 1,603,306 | 3,569,679 | — | — | — | — | — | (6,393,610) | — | (6,393,610) |
| Net change in unrealized holding loss on available-for-sale securities (unaudited) | — | — | — | — | — | — | — | — | — | 29,282 | 29,282 |
| Net loss (unaudited) | — | — | — | — | — | — | — | — | (19,736,940) | — | (19,736,940) |
| Comprehensive loss (unaudited) | — | — | — | — | — | — | — | — | — | — | (19,707,658) |
| Balances at September 30, 2004 (unaudited) | \$29,749,180 | \$39,087,725 | \$67,723,100 | 1,887,356 | \$ 1,888 | \$1,225,177 | \$ 213,710 | \$ — | \$(117,834,669) | \$ — | \$(116,393,894) |

See accompanying notes.

Targacept, Inc.
Statements of Cash Flows

| | Year ended December 31, | | | Nine months ended September 30, | |
|--|-------------------------|----------------------|----------------------|------------------------------------|----------------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| | (unaudited) | | | | |
| Operating activities | | | | | |
| Net loss | \$ (7,302,270) | \$ (21,071,706) | \$ (19,395,321) | \$ (14,347,926) | \$ (19,736,940) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | | | |
| Depreciation and amortization | 308,594 | 958,105 | 672,927 | 502,780 | 564,010 |
| Loss on disposal of equipment | — | 53,996 | — | — | 3,843 |
| Write-off of in-process research and development | — | 2,666,000 | — | — | — |
| Non-cash compensation expense | 92,638 | 129,710 | 65,325 | 43,131 | 32,700 |
| Recognition of deferred rent incentive | — | (167,769) | (402,647) | (301,986) | (301,986) |
| Realized loss on sale of investments | — | — | 20,978 | — | 99,023 |
| Amortization of discount on held-to-maturity investments | (460,701) | (48,446) | — | — | — |
| Changes in operating assets and liabilities, excluding the effects from acquired assets and liabilities: | | | | | |
| Research fees and accounts receivable | (210,448) | (713,109) | 517,030 | 187,621 | 613,290 |
| Inventories | — | 22,464 | 51,016 | 12,464 | 12,245 |
| Prepaid expenses and accrued interest receivable | (555,929) | 158,605 | (205,054) | 70,961 | (885,121) |
| Accounts payable and accrued expenses | 742,837 | 1,503,132 | (326,451) | (1,107,816) | 979,062 |
| Deferred license fee revenue | 1,321,637 | (634,881) | (269,532) | (202,144) | (202,153) |
| Net cash used in operating activities | (6,063,642) | (17,143,899) | (19,271,729) | (15,142,915) | (18,822,027) |
| Investment activities | | | | | |
| Purchase of investments | (29,284,891) | (11,500,000) | (84,796,103) | (48,500,000) | (6,191,930) |
| Proceeds from sale of investments | 32,700,000 | 26,400,000 | 58,500,000 | 48,503,548 | 37,368,032 |
| Purchase of property and equipment | (1,522,064) | (1,281,840) | (545,254) | (284,707) | (591,539) |
| Proceeds from sale of property and equipment | — | — | — | — | 35,592 |
| Proceeds from rent incentive | — | 2,013,234 | — | — | — |
| Purchase of Inversine product | — | (3,500,000) | — | — | — |
| Net cash provided by (used in) investing activities | 1,893,045 | 12,131,394 | (26,841,357) | (281,159) | 30,620,155 |
| Financing activities | | | | | |
| Proceeds from borrowing of long-term debt | — | 3,000,000 | — | — | 1,027,000 |
| Principal payments on long-term debt | — | (324,891) | (637,483) | (436,471) | (511,606) |
| Proceeds from issuance of redeemable convertible preferred stock, net of transaction costs | 96,692 | 45,487,771 | 13,767,452 | 13,767,452 | — |
| Proceeds from issuance of common stock | 106,371 | 48,465 | 238,954 | 173,147 | 502,607 |
| Net cash provided by (used in) financing activities | 203,063 | 48,211,345 | 13,368,923 | 13,504,128 | 1,018,001 |
| Net (decrease) increase in cash and cash equivalents | (3,967,534) | 43,198,840 | (32,744,163) | (1,919,946) | 12,816,129 |
| Cash and cash equivalents at beginning of period | 5,122,014 | 1,154,480 | 44,353,320 | 44,353,320 | 11,609,157 |
| Cash and cash equivalents at end of period | \$ 1,154,480 | \$ 44,353,320 | \$ 11,609,157 | \$ 42,433,374 | \$ 24,425,286 |

See accompanying notes.

Targacept, Inc.
Notes to Financial Statements
December 31, 2003

1. The Company and Nature of Operations

Targacept, Inc., a Delaware corporation (the "Company"), was formed on March 7, 1997. The Company is a biopharmaceutical company engaged in the design, discovery and development of a new class of drugs to treat multiple diseases and disorders by selectively targeting a class of receptors known as neuronal nicotinic acetylcholine receptors, or NNRs. Its facilities are located in Winston-Salem, North Carolina.

The accompanying financial statements have been prepared on a going concern basis. The Company has incurred operating losses since its inception and expects to incur substantial additional losses for the foreseeable future. As a result, the Company will require substantial additional funds, and plans to seek collaborative agreements, research funding, and private or public equity or debt financing to meet such needs. If such funds are not available, management may need to reassess its plans. Even if the Company does not have an immediate need for additional cash, it may seek access to the private or public equity markets if and when conditions are favorable. There is no assurance that such additional funds will be available for the Company to finance its operations on acceptable terms, if at all.

The accompanying balance sheet as of September 30, 2004, the statements of operations and statements of cash flows for the nine months ended September 30, 2003 and 2004 and the statement of redeemable convertible preferred stock and stockholders' equity (deficit) for the nine months ended September 30, 2004 are unaudited. The unaudited interim financial statements have been prepared on the same basis as the annual financial statements and, in the opinion of the Company's management, reflect all adjustments, which include only normal recurring adjustments necessary to present fairly the Company's financial position and results of operations and cash flows for the nine months ended September 30, 2003 and 2004. The financial data and other information disclosed in these notes to financial statements related to the nine-month periods are unaudited. The results for the nine months ended September 30, 2004 are not necessarily indicative of the results to be expected for the year ending December 31, 2004 or for any other interim period or for any other future year.

2. Summary of Significant Accounting Policies

Cash and Cash Equivalents

The Company considers cash equivalents to be those investments, which are highly liquid, readily convertible to cash, and which mature within three months from the date of purchase.

Investments

In accordance with the Company's investment policy, surplus cash is invested with high quality financial institutions in money market accounts, certificates of deposit, and a mutual fund that invests in Government National Mortgage Association and other mortgage-backed securities, United States Government debt and other asset-backed securities with AAA credit ratings. The Company determines the appropriate classification of marketable securities at the time of purchase and reevaluates such designation as of each balance sheet date. All marketable securities have been classified as available-for-sale and are stated at market value with the unrealized holding gains and losses reported as a component of stockholders' equity in comprehensive loss. Interest and dividend income on investments, as well as realized gains and losses, are included in "Interest and dividend income." The cost of securities sold is based on the specific identification method.

Research Fees and Accounts Receivable

Substantially all of the Company's research fees and accounts receivable are related to the collaborative research and license agreements discussed in Note 15, and trade sales of Inversine. All of the Company's trade

Targacept, Inc.

Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

accounts receivable are due from customers located within the United States. The Company makes judgments with respect to the collectibility of trade accounts receivable based on historical experience and current economic trends. Actual losses could differ from those estimates.

During 2001, 2002, 2003 and the nine months ended September 30, 2004, the Company recognized revenues of \$1,703,000, \$2,024,000, \$1,572,000 and \$411,000, respectively, or 99%, 89%, 64% and 26%, respectively, of net revenues, from two collaborative research and license agreements discussed in Note 15.

Inventories

Inventories are stated at the lower of cost or market. Cost is determined by the weighted-average method.

Property and Equipment and Intangible Assets

Property and equipment consists primarily of lab equipment, office furniture and fixtures and leasehold improvements and is recorded at cost. Depreciation is computed using the straight-line method over the estimated useful lives of the assets ranging from three to ten years. Lab equipment is typically depreciated over 3-5 years, office furniture and fixtures are typically depreciated over 7-10 years, and leasehold improvements are amortized over the life of the applicable lease.

Intangible assets consist of patents acquired (See Note 16). The intangible assets are being amortized to research and development expense on a straight-line basis over the remaining useful life of the patents, or a period of 17 years from the date of acquisition.

The Company assesses the net realizable value of its long-lived assets and evaluates such assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of an asset may not be recoverable. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of the asset and its eventual disposition are less than its carrying amount. An impairment loss, if recognized, would be based on the excess of the carrying value of the impaired asset over its respective fair value. Through September 30, 2004, there has been no such impairment.

Patents

The Company capitalizes the costs of patents purchased from external sources. The Company expenses all other patent-related costs.

Research and Development Costs

Research and development costs are expensed as incurred and include related salaries of personnel involved in research and development activities, contractor fees, administrative expenses and allocations of research-related overhead costs. Administrative expenses and research-related overhead costs included in research and development consist of allocations of facility and equipment lease charges, depreciation and amortization of assets, and insurance, legal and supply costs that are directly related to research and development activities.

The Company directly reduces research and development expenses for amounts reimbursed pursuant to cost-sharing agreements. During 2001, 2002 and 2003 and the nine months ended September 30, 2004, research and development expenses were reduced by \$412,000, \$514,000, \$131,000 and \$95,000, respectively, for costs reimbursed primarily by Dr. Falk Pharma, GmbH and under the terms of the collaboration described in Note 15.

Targacept, Inc.

Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

Clinical Trials Accounting

The Company records accruals based on estimates of the services received, efforts expended and amounts owed pursuant to contracts with numerous clinical trial centers and contract research organizations. In the normal course of business, the Company contracts with third parties to perform various clinical trial activities in the ongoing development of potential products. The financial terms of these agreements are subject to negotiation and variation from contract to contract and may result in uneven payment flows. Payments under the contracts depend on factors such as the achievement of certain events, the successful recruitment of patients, the completion of portions of the clinical trial or similar conditions. The objective of the Company's accrual policy is to match the recording of expenses in its financial statements to the actual services received and efforts expended. As such, expense accruals related to clinical trials are recognized based on the Company's estimate of the degree of completion of the event or events specified in the specific clinical study or trial contract.

Deferred Rent Incentive

In August 2002, the Company received \$2,013,000 as an incentive to lease its current office space. The incentive is being recognized monthly over the life of the lease on a straight-line basis as a reduction to the lease expense in general and administrative expenses. The Company recognized \$168,000, \$403,000 and \$302,000 of the incentive during 2002, 2003 and the nine months ended September 30, 2004, respectively.

Redeemable Convertible Preferred Stock

The carrying value of redeemable convertible preferred stock is increased by periodic accretions so that the carrying amount will equal the redemption amount at the earliest redemption date. These increases are affected through charges to accumulated deficit.

Fair Value of Financial Instruments

The carrying amounts of cash and cash equivalents, short-term investments, accounts receivable, accounts payable, accrued expenses and redeemable convertible preferred stock are considered to be representative of their respective fair values. The fair value of long-term debt is \$2,590,000, \$1,961,000 and \$2,495,000 at December 31, 2002, 2003 and September 30, 2004, respectively. The Company estimates the fair value of long-term debt using discounted cash flows based on its incremental borrowing rates for similar debt.

Credit Risk

Financial instruments that potentially subject the Company to credit risk consist principally of cash and short-term investments. The Company places its cash and cash equivalents with high-credit quality financial institutions. The Company has established guidelines for investment of its excess cash designed to emphasize safety, liquidity and preservation of capital.

Revenue Recognition

The Company uses revenue recognition criteria in Staff Accounting Bulletin No. 101, *Revenue Recognition in Financial Statements*, as amended by Staff Accounting Bulletin No. 104, *Revision of Topic 13*. Revenues are recorded under collaboration agreements at the time of performance of services. Research fee revenues are earned and recognized in accordance with contract provisions. License fees for access to the Company's

Targacept, Inc.

Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

intellectual properties are recognized ratably over the contracted period in accordance with the provisions of the contract. Amounts received in advance of performance are recorded as deferred revenue and amortized in the statements of operations into revenue over the estimated life of the research and development period. Revenues from milestones are only recognized upon achievement of the milestone criteria. Product sales revenues are recorded when goods are shipped, at which point title has passed.

Shipping and Handling Costs

During 2002, 2003 and the nine months ended September 30, 2004, \$22,000, \$173,000 and \$129,000 respectively, of shipping and handling costs were included in cost of product sales.

Income Taxes

The liability method is used in accounting for income taxes as required by Statement of Financial Accounting Standards (“SFAS”) No. 109, *Accounting for Income Taxes*. Under this method, deferred tax assets and liabilities are recognized for operating loss and tax credit carryforwards and for the future tax consequences attributable to the differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in the results of operations in the period that includes the enactment date. A valuation allowance is recorded to reduce the carrying amounts of deferred tax assets unless it is more likely than not that such assets will be realized. Currently there is no provision for income taxes as the Company has incurred net losses to date.

Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income*, requires components of other comprehensive loss, including unrealized gains and losses on available-for-sale securities, to be included as part of total comprehensive loss. The components of comprehensive loss are included in the statements of redeemable convertible preferred stock and stockholders’ equity (deficit).

Net Loss Per Share Attributable to Common Stockholders

The Company computes net loss per share attributable to common stockholders in accordance with SFAS No. 128, *Earnings Per Share* (“SFAS 128”). Under the provisions of SFAS 128, basic net loss per share attributable to common stockholders (“Basic EPS”) is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding. Diluted net loss per share attributable to common stockholders (“Diluted EPS”) is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares and dilutive common share equivalents then outstanding. Common share equivalents consist of the incremental common shares issuable upon the conversion of preferred stock, shares issuable upon the exercise of stock options and shares issuable upon the exercise of warrants. For the periods presented, Diluted EPS is identical to Basic EPS because common share equivalents are excluded from the calculation, as their effect is antidilutive.

Pro Forma Stockholders’ Equity and Pro Forma Net Loss Per Share

The Company’s Board of Directors has authorized management of the Company to file a registration statement with the Securities and Exchange Commission permitting the Company to sell shares of its common stock to the public in an initial public offering (the “IPO”). If the IPO is closed under the terms presently

Targacept, Inc.
Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

anticipated, all of the redeemable convertible preferred stock outstanding at the time of the IPO will automatically convert into 73,739,905 shares of common stock. Unaudited pro forma stockholders' equity, as adjusted for the assumed conversion of the preferred stock, is set forth on the accompanying balance sheets. Unaudited pro forma basic and diluted net loss per share is computed using the weighted average number of common shares outstanding, including the pro forma effects of the conversion of outstanding redeemable convertible preferred stock into shares of the Company's common stock effective upon the completion of the Company's planned IPO as if such conversion had occurred at January 1, 2003, or the date of issuance, if later.

The following table sets forth the computation of basic and diluted, and unaudited pro forma basic and diluted, net loss per share attributable to common stockholders:

| | Year ended December 31, | | | Nine months ended September 30, | |
|---|-------------------------|-----------------|-----------------|------------------------------------|-----------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| | | | | (unaudited) | |
| Historical | | | | | |
| Numerator: | | | | | |
| Net loss attributable to common stockholders | \$ (11,110,258) | \$ (25,245,251) | \$ (27,735,949) | \$ (20,546,662) | \$ (26,162,608) |
| Denominator: | | | | | |
| Weighted-average common shares outstanding | 414,624 | 557,492 | 817,894 | 759,937 | 1,555,090 |
| Basic and diluted net loss per share attributable to common stockholders | \$ (26.80) | \$ (45.28) | \$ (33.91) | \$ (27.04) | \$ (16.82) |
| Pro forma | | | | | |
| Numerator: | | | | | |
| Net loss attributable to common stockholders | | | \$ (19,395,321) | | \$ (19,736,940) |
| Denominator: | | | | | |
| Shares used above | | | 817,894 | | 1,555,090 |
| Pro forma adjustments to reflect assumed conversion of preferred stock, on a weighted average basis (unaudited) | | | 70,300,735 | | 73,739,905 |
| Shares used to compute pro forma basic and diluted net loss per share attributable to common stockholders (unaudited) | | | 71,118,629 | | 75,294,995 |
| Pro forma basic and diluted net loss per share attributable to common stockholders (unaudited) | | | \$ (0.27) | | \$ (0.26) |

Targacept, Inc.

Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

The Company has excluded all outstanding stock options and warrants from the calculation of net loss per share attributable to common stockholders because such securities are antidilutive for all periods presented. Had the Company been in a net income position, these securities may have been included in the calculation. These potentially dilutive securities consist of the following on a weighted average basis:

| | Year Ended December 31, | | | Nine Months ended September 30, | |
|--|-------------------------|-------------------|-------------------|---------------------------------|-------------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| Outstanding common stock options | 1,496,707 | 2,150,650 | 4,601,270 | 3,918,198 | 7,637,869 |
| Redeemable convertible preferred stock | 11,567,567 | 15,980,048 | 70,300,735 | 69,141,747 | 73,739,905 |
| Outstanding warrants | 1,612,903 | 1,612,903 | 1,612,903 | 1,612,903 | 1,612,903 |
| Total | 14,677,177 | 19,743,601 | 76,514,908 | 74,672,848 | 82,990,677 |

Stock-Based Compensation

In December 2002, the Financial Accounting Standards Board (“FASB”) issued SFAS No. 148, *Accounting for Stock-Based Compensation—Transition and Disclosure*. SFAS No. 148 amends SFAS No. 123 to provide alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation. In addition, SFAS No. 148 amends the disclosure provisions of SFAS No. 123 and Accounting Principles Board (“APB”) Opinion No. 28, *Interim Financial Reporting*, to require more prominent disclosure in the summary of significant accounting policies about the method of accounting for the effects of an entity’s accounting policy with respect to stock-based employee stock compensation and the effect of the method used on reported net loss results.

The Company has elected to continue to account for stock options granted to employees using the intrinsic-value method as prescribed by APB Opinion No. 25, *Accounting for Stock Issued to Employees*, and, thus recognizes no compensation expense for options granted with exercise prices equal to the fair market value of the Company’s common stock on the date of grant. The information regarding net loss as required by SFAS No. 123 has been determined as if the Company had accounted for its employee stock options under the fair value method of that Statement.

The following table illustrates the weighted-average assumptions for the Black-Scholes model used in determining the fair value of options granted to employees:

| | Year ended December 31, | | | Nine months ended September 30, | |
|-------------------------|-------------------------|---------|---------|---------------------------------|---------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| Dividend yield | — | — | — | — | — |
| Risk-free interest rate | 4.0% | 3.5% | 2.8% | 2.5% | 2.7% |
| Volatility | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Expected life | 4 years | 4 years | 4 years | 4 years | 4 years |

Targacept, Inc.
Notes to Financial Statements—(continued)
2. Summary of Significant Accounting Policies (continued)

For purposes of disclosures pursuant to SFAS No. 123, as amended by SFAS No. 148, the estimated fair value of the options is amortized to expense over the options' vesting period. The following table illustrates the effect on net loss if the Company had applied the fair value recognition provisions of SFAS No. 123:

| | Year Ended December 31, | | | Nine months ended September 30, | |
|---|-------------------------|-----------------|-----------------|------------------------------------|-----------------|
| | 2001 | 2002 | 2003 | 2003 | 2004 |
| Net loss attributable to common stockholders, as reported | \$ (11,110,258) | \$ (25,245,251) | \$ (27,735,949) | \$ (20,546,662) | \$ (26,162,608) |
| Add: Stock-based employee compensation expense included in reported net income, net of related tax effects | 92,638 | 129,710 | 65,325 | 43,131 | 32,700 |
| Deduct: Stock-based employee compensation expense determined under fair value based method for all awards, net of related tax effects | (205,710) | (312,830) | (515,405) | (320,882) | (681,777) |
| Pro forma net loss | \$ (11,223,330) | \$ (25,428,371) | \$ (28,186,029) | \$ (20,824,413) | \$ (26,811,685) |
| Net loss per share: | | | | | |
| Basic and diluted, as reported | \$ (26.80) | \$ (45.28) | \$ (33.91) | \$ (27.04) | \$ (16.82) |
| Basic and diluted, pro forma | \$ (27.06) | \$ (45.61) | \$ (34.46) | \$ (27.40) | \$ (17.24) |

Stock compensation arrangements to non-employees are accounted for in accordance with SFAS No. 123, as amended by SFAS No. 148, and EITF No. 96-18, *Accounting for Equity Instruments That Are Issued to Other than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, using a fair value approach.

Recent Accounting Pronouncements

In 2003, FASB Statement No. 150, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity* ("SFAS 150"), was issued. This statement establishes how a company classifies and measures certain financial instruments with characteristics of both liabilities and equity, including redeemable convertible preferred stock. This statement is effective for financial instruments entered into or modified after May 31, 2003, and otherwise effective at the beginning of the interim period commencing July 1, 2003, except for mandatory redeemable financial instruments of nonpublic companies. The FASB has indefinitely deferred implementation of certain provisions of SFAS 150. The adoption of SFAS 150 did not affect the financial position or results of operations of the Company.

In 2003, the FASB issued Interpretation No. 46, *Consolidation of Variable Interest Entities* ("FIN 46"), which is an interpretation of Accounting Research Bulletin No. 51, *Consolidated Financial Statements*. FIN 46 requires that if an entity has a controlling interest in a variable interest entity, the assets, liabilities, and results of activities of the variable interest entity should be included in the consolidated financial statements of the entity. FIN 46 is effective immediately for all new variable interest entities created or acquired after January 31, 2003. The Company implemented the provisions of FIN 46 for its financial statements for the year ending December 31, 2003 for any variable interest entities created before February 1, 2003. The adoption of FIN 46 did not affect the financial position or results of operations of the Company.

In October 2004, the FASB announced that FASB Statement No. 123R, *Share-Based Payment*, which would require all companies to measure compensation cost for all share-based payments, including employee stock

Targacept, Inc.
Notes to Financial Statements—(continued)

2. Summary of Significant Accounting Policies (continued)

options, at fair value, would be effective for public companies for interim or annual periods beginning after June 15, 2005. SFAS 123R would require companies to expense the fair value of all stock options that have future vesting provisions, are modified or are newly granted beginning on the grant date of such options. The Company will evaluate the requirements of the final standard, which is expected to be issued in December 2004, to determine the impact on its financial position and results of operations.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

Reclassifications

Certain reclassifications have been made to the prior year financial statements to conform to the current year presentation. These reclassifications had no impact on net loss or previously recorded amounts.

3. Short-term investments

The following is a summary of available-for-sale securities as of December 31, 2002 and 2003. During 2004, all short-term investments present at December 31, 2003 were converted to cash.

| December 31, 2002 | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|-------------------------|--------------------|---------------------|----------------------|--------------------|
| Certificates of deposit | \$5,000,000 | \$ — | \$ — | \$5,000,000 |
| Interest receivable | 8,139 | — | — | 8,139 |
| Total | \$5,008,139 | \$ — | \$ — | \$5,008,139 |

| December 31, 2003 | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|-------------------------------|---------------------|---------------------|----------------------|---------------------|
| Adjustable rate mortgage fund | \$20,177,033 | \$ — | \$(29,282) | \$20,147,751 |
| Certificates of deposit | 11,098,092 | — | — | 11,098,092 |
| Interest receivable | 121,657 | — | — | 121,657 |
| Total | \$31,396,782 | \$ — | \$(29,282) | \$31,367,500 |

The adjustable rate mortgage fund investment has remained in an unrealized loss position for less than 6 months. Accordingly the Company believes this is a temporary decline. The Company recognized \$1,448,000, \$88,000, \$591,000 and \$159,000 of interest income during 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively. The Company recognized \$200,000 and \$193,000 of dividend income during 2003 and the nine months ended September 30, 2004, respectively.

4. Inventories

Inventories consisted of the following:

| | December 31, | | September 30, |
|-----------------|------------------|------------------|-------------------|
| | 2002 | 2003 | 2004 |
| Raw materials | \$137,706 | \$ 46,988 | \$ 46,988 |
| Work-in-process | 9,042 | 6,892 | 6,400 |
| Finished goods | 22,788 | 64,640 | 52,887 |
| | \$169,536 | \$118,520 | \$ 106,275 |

Targacept, Inc.
Notes to Financial Statements—(continued)

5. Property and equipment

Property and equipment consists of the following:

| | December 31, | | September 30, |
|--------------------------------|---------------------|---------------------|---------------------|
| | 2002 | 2003 | 2004 |
| Lab equipment | \$ 4,674,369 | \$ 5,057,345 | \$ 4,746,687 |
| Office furniture and fixtures | 1,030,406 | 1,192,685 | 1,426,680 |
| Leasehold improvements | 87,875 | 87,875 | 132,941 |
| | <u>5,792,650</u> | <u>6,337,905</u> | <u>6,306,308</u> |
| Less: accumulated depreciation | 3,329,706 | 3,964,870 | 3,916,856 |
| Property and equipment, net | <u>\$ 2,462,944</u> | <u>\$ 2,373,035</u> | <u>\$ 2,389,452</u> |

The Company recorded \$309,000, \$577,000, \$635,000 and \$536,000 of depreciation expense during 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively.

6. Intangible Assets

Intangible assets consist of the following:

| | December 31, | | September 30, |
|--------------------------------|------------------|------------------|-------------------|
| | 2002 | 2003 | 2004 |
| Patents (See Note 16) | \$642,000 | \$642,000 | \$ 642,000 |
| Less: accumulated amortization | (15,735) | (53,499) | (81,822) |
| Total | <u>\$626,265</u> | <u>\$588,501</u> | <u>\$ 560,178</u> |

The Company recognized amortization expense of \$0, \$16,000, \$38,000 and \$28,000 in 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively. The Company expects to recognize \$38,000 of amortization expense in each of the next five years.

7. Accrued Expenses

Accrued expenses consists of the following:

| | December 31, | | September 30, |
|-----------------------|---------------------|---------------------|---------------------|
| | 2002 | 2003 | 2004 |
| Clinical trials costs | \$ 361,119 | \$ 623,158 | \$ 935,058 |
| Employee compensation | 860,368 | 676,900 | 759,301 |
| Other | 255,547 | 106,720 | 64,920 |
| | <u>\$ 1,477,034</u> | <u>\$ 1,406,778</u> | <u>\$ 1,759,279</u> |

8. Long-term debt

During 2002, the Company entered into agreements to borrow \$500,000 from the City of Winston-Salem and \$2,500,000 from R.J. Reynolds Tobacco Company ("RJRT"). The note payable to the City of Winston-Salem matures on April 19, 2012, is non-interest bearing until April 2007 and, thereafter, bears interest between 5% and 7% depending on the gross revenues of the Company until maturity. No payments are due on the City of

Targacept, Inc.
Notes to Financial Statements—(continued)

8. Long-term debt (continued)

Winston-Salem note until the 5-year anniversary of the loan. The note payable to RJRT accrues interest at 6.6%, is repayable in monthly payments of \$59,403 through the maturity date of May 1, 2006, and is secured by equipment owned by the Company with a book value of approximately \$2,373,000, net of accumulated depreciation, at December 31, 2003. In January 2004, the Company amended the note agreement with RJRT to allow for up to three additional tranches to be advanced to the Company for up to a total of \$2,000,000. Each of the additional tranches will accrue interest at the 4-year U.S. Treasury rate plus 3.5% determined on the day the additional tranche is advanced and will be repayable in 48 equal monthly installments. The Company was advanced an additional tranche on April 1, 2004 in the amount of \$1,027,000. This additional tranche accrues interest at 5.87% and is repayable in monthly payments of \$24,000 through the maturity date of April 1, 2008. The Company paid \$91,000, \$135,000 and \$84,000 for interest under the RJRT note during 2002, 2003 and the nine months ended September 30, 2004, respectively.

Maturities of long-term debt are as follows:

| | Maturities as of | |
|------------|----------------------|-----------------------|
| | December 31, 2003 | September 30, 2004 |
| 2004 | \$ 576,072 | \$ 219,372 |
| 2005 | 669,379 | 913,378 |
| 2006 | 292,175 | 550,889 |
| 2007 | 69,438 | 343,753 |
| 2008 | 93,830 | 188,896 |
| Thereafter | 336,732 | 336,732 |
| | <u>\$ 2,037,626</u> | <u>\$ 2,553,020</u> |

See Note 18—Subsequent Events.

9. Redeemable Preferred Stock

In August 2000, the Company issued 5,000,000 shares of its Series A redeemable convertible preferred stock (the “Series A”) to RJRT, and completed a private placement of 6,537,634 of its Series B redeemable convertible preferred stock (the “Series B”) generating cash of \$29,073,000, net of offering costs.

In January 2001, the Company issued 29,933 shares of Series B to three consultants in partial payment of consulting fees owed by the Company.

In November 2002, the Company completed a private placement of 37,764,180 shares of its Series C redeemable convertible preferred stock (the “Series C”) and received cash of \$45,488,000, net of offering costs.

In March 2003, the Company completed a private placement of an additional 11,404,958 shares of Series C and received cash of \$13,767,452, net of offering costs.

See Note 18—Subsequent Events.

The following is a summary of the rights, preferences and terms of the Company’s outstanding series of redeemable convertible preferred stock:

Conversion

Each share of Series A, Series B and Series C is convertible, at the option of the holder thereof, at any time and from time to time, and without the payment of additional consideration by the holder thereof, into fully paid and nonassessable shares of the Company’s common stock. As of December 31, 2003 and September 30, 2004, conversion of the Series A, Series B and Series C would result in the issuance of 5,000,000, 15,619,675, and 53,120,230 shares of common stock, respectively. Future sales of equity at prices below the respective

Targacept, Inc.
Notes to Financial Statements—(continued)

9. Redeemable Preferred Stock (continued)

conversion prices could result in adjustments to the number of shares of common stock into which each series of preferred stock is convertible.

Automatic conversion of the Series A, Series B and Series C into fully paid and nonassessable shares of common stock, without the payment of additional consideration by the holders thereof, would occur immediately upon the closing of the sale of the Company's common stock in a firm commitment, underwritten public offering registered under the Securities Act of 1933 in which (i) the price per share equals or exceeds \$3.60 (subject to certain adjustments) and (ii) the gross proceeds to the Company are not less than \$50,000,000. The accrued but unpaid cumulative dividend on the Series C shall, if not yet declared, be forfeited upon conversion of the Series C.

Dividends

Dividends accrue daily on each share of Series C on a cumulative basis at the rate of 8% per annum and are recorded as an increase to Series C and an increase to accumulated deficit. Cumulative dividends may be declared and paid at any time and shall be payable upon liquidation or redemption. At December 31, 2003 and September 30, 2004, cumulative accrued dividends on the Series C stock totaled \$4,898,000 and \$8,468,000, respectively.

Dividends on the Series A, Series B and Series C are payable when and if declared by the Board of Directors. No dividend may be paid on the common stock without the approval of the holders of a majority of the then outstanding shares of Series A and Series B, considered together on an as-converted basis, and the holders of 65% of the Series C. No dividend may be declared or paid on either the Series A or the Series B unless, simultaneously with such declaration or payment, the same dividend per share is declared or paid on both the Series A and the Series B, as well as the Series C, and any unpaid cumulative dividends on the Series C are declared and paid in full.

Voting

Each holder of the Series A, Series B and Series C is entitled to the number of votes equal to the number of shares of common stock into which such holder's shares are convertible on the applicable record date. In addition, certain actions by the Company require the approval of one or more of (i) the holders of a majority of the outstanding shares of Series A, (ii) the holders of at least two-thirds of the outstanding shares of Series B, (iii) the holders of a majority of the outstanding shares of Series A and Series B, considered together on an as-converted basis, and/or (iv) the holders of at least 65% of the outstanding shares of Series C.

Liquidation Preference

In the event of any liquidation, dissolution or winding up of the Company, the holders of the Series C shares have preference and are entitled to receive an amount per share equal to the greater of (i) their initial purchase price per share plus any accrued or declared and unpaid dividends on such share or (ii) the amount per share of Series C that such holders would receive if all of the Series A, Series B and Series C were converted to common stock immediately prior to such liquidation, dissolution or winding up.

Next, the holders of Series A and Series B are entitled to receive, on a *pari passu* basis, an amount equal to their initial purchase price per share plus any declared and unpaid dividends on such shares. Any assets of the Company remaining after the payments specified above shall be distributed on a *pari passu* basis among the holders of common stock and, on an as-converted to common stock basis, Series A, Series B and Series C. Unless the holders of a prescribed number of shares of Series A, Series B and/or Series C otherwise elect, certain

Targacept, Inc.
Notes to Financial Statements—(continued)

9. Redeemable Preferred Stock (continued)

fundamental transactions involving the Company shall be treated as a liquidation for the Series A, Series B and/or Series C, as the case may be.

Mandatory Redemption

At any time after November 26, 2008, upon demand by the holders of at least 65% of the outstanding shares of Series C, all of the outstanding shares of Series C shall be redeemed in cash in an amount per share equal to the initial purchase price per share (subject to certain adjustments) plus any accrued or declared and unpaid dividends on such shares.

At any time after the later of August 22, 2005 or the date on which no shares of Series C are outstanding, a number of outstanding shares of Series A or Series B elected upon demand by the holders of a majority of the outstanding shares of Series A (in the case of Series A) or a majority of the outstanding shares of Series B (in the case of Series B) shall be redeemed in an amount per share equal to \$4.65 (subject to certain adjustments) plus (i) any previously declared but unpaid dividends on such share and (ii) an amount equal to \$0.081375 per share (subject to certain adjustments) multiplied by the number of complete three-month periods that have elapsed from the date such share was originally issued to the redemption date. The Company may satisfy its redemption obligation with respect to the Series A and/or the Series B in cash or by paying a portion in cash and issuing a promissory note that meets certain prescribed conditions for the remaining amount.

10. Stockholders' Equity (Deficit)

Prior to August 22, 2000, the Company was a wholly owned subsidiary of RJRT. On August 22, 2000, the Company reclassified its 500 shares of common stock as 5,000,000 shares of Series A and a warrant to purchase 1,612,903 shares of the Company's common stock at \$4.65 per share. The fair value of the Series A redeemable convertible preferred stock was determined to be \$4.65 per share based on the sales price of Series B of \$4.65 per share redeemable convertible preferred stock with rights containing identical terms as Series A. As cash was not received in connection with this reclassification of the 500 shares of common stock into shares of Series A redeemable convertible preferred stock, the fair value of \$23,250,000 was recorded as redeemable convertible preferred stock. On the same date, the Company sold 5,892,473 shares of the Company's Series B to an investor group. The Company then issued 309,424 shares of the common stock to management, at par value, for proceeds of \$309, which was less than fair value. As a result, the Company recorded compensation expense of \$145,120. An aggregate of 645,161 shares of Series B redeemable convertible preferred stock were subsequently sold in a second offering to certain of the Company's investors.

On January 2, 2001, the Company amended its Certificate of Incorporation to increase the number of authorized shares of preferred stock to 11,567,567 shares and issued 29,933 shares of Series B to consultants in exchange for the partial satisfaction of a cash liability on January 26, 2001.

On November 26, 2002, the Company amended its Certificate of Incorporation to increase the number of authorized shares of common stock to 75,000,000 and preferred stock to 49,331,747 and issued 37,764,180 shares of Series C.

On March 14, 2003, the Company amended its Certificate of Incorporation to increase the number of authorized shares of common stock to 85,000,000 and preferred stock to 60,736,705 and issued 11,404,958 shares of Series C.

In conjunction with the issuance of Series A, the Company issued a warrant to purchase 1,612,903 shares of the Company's common stock at an original exercise price of \$4.65 per share (subject to certain adjustments). In

Targacept, Inc.
Notes to Financial Statements—(continued)

10. Stockholders' Equity (Deficit) (continued)

connection with the Company's issuance of Series C and price adjustment provisions of the warrant, the conversion price of the warrant was adjusted to \$1.95. The warrant is exercisable only upon the earlier of an initial public offering or a change in control. The fair value of the warrant is a direct cost of obtaining capital. As such, the fair value has been recorded in stockholders' equity, with the offset recorded as a decrease in the redemption value of the Series A. The Company will accrete to the redemption value of the Series A at the earliest date of redemption, or until August 2005 through an increase in redemption value to Series A and an increase to retained deficit. The fair value of the warrant to purchase 1,612,903 shares of the Company's common stock was estimated at the grant date to be \$213,710 or \$0.53 per share. The Company considered the anti-dilution features, the contingencies surrounding the limited opportunities for exercise, and the warrant's priorities over common stock options in relation to the fair value of the Company's common stock at the date of issuance when estimating the fair value of the warrant.

At December 31, 2003 and September 30, 2004, the Company had reserved shares of common stock for future issuance as follows:

| | December 31, 2003 | September 30, 2004 |
|-----------------------------|----------------------|-----------------------|
| Convertible preferred stock | 73,739,905 | 73,739,905 |
| Warrant | 1,612,903 | 1,612,903 |
| Options | 8,554,421 | 7,749,836 |
| | <u>83,907,229</u> | <u>83,102,644</u> |

11. Income Taxes

There is no income tax provision (benefit) for federal or state income taxes as the Company has incurred operating losses since inception.

The Company's effective tax rate differs from the federal income tax rate for the following reasons:

| | Year ended December 31, | | | Nine months ended September 30, |
|---|-------------------------|-----------|-----------|------------------------------------|
| | 2001 | 2002 | 2003 | 2004 |
| Expected federal income tax benefit at statutory rate | (34)% | (34)% | (34)% | (34)% |
| Increase (decrease) resulting from: | | | | |
| Research and development credits | — | (1) | (6) | (3) |
| Purchased in-process research and development | — | 4 | — | — |
| State income tax expense, net of federal benefit | (5) | (4) | (5) | (5) |
| Net operating loss and credit limitations | — | 14 | 3 | — |
| Change in valuation allowance | 38 | 21 | 41 | 42 |
| Other | 1 | — | 1 | — |
| | <u>—%</u> | <u>—%</u> | <u>—%</u> | <u>—%</u> |

At December 31, 2002 and 2003 and September 30, 2004, the Company had net operating loss carryforwards for federal income tax purposes of approximately \$17,637,000, \$38,409,000 and \$57,489,000, respectively, \$25,317,000, \$46,090,000 and \$65,170,000, respectively, for state income tax purposes, and research and development tax credits of approximately \$299,000, \$1,456,000 and \$1,202,000, respectively. The federal net operating loss carryforwards begin to expire in 2020. State net operating loss carryforwards begin to expire in 2015. The research and development tax credits will begin to expire in 2021.

Targacept, Inc.
Notes to Financial Statements—(continued)

11. Income Taxes (continued)

Utilization of the net operating loss carryforwards and credits may be subject to a substantial annual limitation due to ownership change limitations provided by Section 382 of the Internal Revenue Code of 1986, as amended, and similar state provisions. As a result of a series of stock issuances, the Company had such an ownership change on November 30, 2002. Consequently, an annual limitation is imposed on the Company's use of net operating loss and credit carryforwards attributable to periods before the change.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The Company's net deferred tax assets relate primarily to its net operating loss carryforwards. A valuation allowance has been recognized to offset the deferred tax assets related primarily to its net operating loss carryforward. If and when recognized, the tax benefit for those items will be reflected in current operations of the period in which the benefit is recorded as a reduction of income tax expense. The utilization of the loss carryforwards to reduce future income taxes will depend on the Company's ability to generate sufficient taxable income prior to the expiration of the net operating loss carryforwards. For the years ended December 31, 2002, 2003 and the nine months ended September 30, 2004, the valuation allowance increased approximately \$7,380,000, \$8,617,000 and \$4,736,000, respectively.

Significant components of the Company's deferred tax assets (liabilities) are as follows:

| | December 31, | | September 30, |
|--|------------------|-------------------|-------------------|
| | 2002 | 2003 | 2004 |
| Deferred tax assets: | | | |
| Net operating loss carryforward | \$ 7,149,405 | \$ 15,158,059 | \$ 22,514,223 |
| Research and development tax credit | 48,153 | 638,153 | 1,202,482 |
| Equipment and other | 226,338 | — | — |
| Patents | 682,413 | 641,008 | 557,356 |
| Unearned revenue | 843,084 | 739,167 | 661,229 |
| Total gross deferred tax assets | 8,949,393 | 17,176,387 | 24,935,290 |
| Valuation allowance | (8,949,393) | (16,999,275) | (24,782,695) |
| Net deferred tax asset | — | 177,112 | 152,595 |
| Deferred tax liabilities: | | | |
| Equipment and other | — | (177,112) | (152,595) |
| Net deferred tax asset | \$ — | \$ — | \$ — |

12. Equity Incentive Plan

On August 22, 2000, the Company established an Equity Incentive Plan (the "Plan") and authorized the issuance of up to 2,011,259 shares under the Plan to attract and retain employees, directors and certain independent contractors, consultants and advisors and to allow them to participate in the growth of the Company. During 2001, the number of shares authorized for issuance under the Plan was increased to 2,611,259. In conjunction with the Series C financing, the Company authorized the issuance of an additional 3,000,000 shares, increasing the number of authorized shares to 5,611,259. Upon the issuance of the additional Series C shares in March 2003, the number of authorized shares was increased to 9,216,657. Awards may be made to participants under the Plan in the form of incentive and nonqualified stock options, restricted stock, stock appreciation rights,

Targacept, Inc.
Notes to Financial Statements—(continued)

12. Equity Incentive Plan (continued)

stock awards, and performance awards. Eligible participants under the Plan include employees, directors and certain independent contractors, consultants or advisors of the Company or a related corporation. The vesting periods for awards made under the Plan are determined at the discretion of the Plan administrator. The exercise price of incentive options granted under the Plan may not be less than 100% of the fair market value of the common stock on the date of grant, as determined by the Plan Administrator. The following summarizes stock option activity and balances:

| | Options Granted | Price | Weighted Average Exercise Price Per Share |
|-----------------------------------|--------------------|-------------|---|
| Outstanding at January 1, 2001 | 1,234,999 | 0.47 | \$ 0.47 |
| Granted | 440,000 | 0.47-4.65 | 0.90 |
| Forfeited | (31,717) | 0.47 | 0.47 |
| Exercised | (65,565) | 0.47 | 0.47 |
| Outstanding at December 31, 2001 | 1,577,717 | 0.47-4.65 | 0.59 |
| Granted | 838,550 | 0.01-0.68 | 0.58 |
| Forfeited | (18,672) | 0.56 | 0.56 |
| Exercised | (90,984) | 0.47-0.68 | 0.53 |
| Outstanding at December 31, 2002 | 2,306,611 | 0.47-4.65 | 0.59 |
| Granted | 5,996,095 | 0.01-0.75 | 0.67 |
| Forfeited | (35,980) | 0.01-0.68 | 0.26 |
| Exercised | (458,187) | 0.01-0.68 | 0.52 |
| Outstanding at December 31, 2003 | 7,808,539 | 0.01-0.75 | 0.65 |
| Granted | 381,900 | 0.01-0.75 | 0.70 |
| Forfeited | (35,543) | 0.68-4.65 | 3.47 |
| Exercised | (804,585) | 0.47-0.75 | 0.62 |
| Outstanding at September 30, 2004 | 7,350,311 | \$0.01-0.75 | \$ 0.64 |

The weighted average fair value of options granted during 2001, 2002, 2003 and the nine months ended September 30, 2004 was \$0.38, \$0.46, \$0.41 and \$0.47, respectively. At December 31, 2001, 2002, 2003 and September 30, 2004, 83,305, 958,059, 3,538,218 and 4,118,303 options, respectively, were exercisable at a weighted-average price of \$0.47, \$0.64, \$0.63 and \$0.62, respectively.

A summary of options outstanding as of December 31, 2003 is as follows:

| Exercise Price | Options Outstanding | | | Options Exercisable | |
|----------------|---------------------|--|---------------------------------|---------------------|------------------------|
| | Number Outstanding | Weighted Average Remaining Contractual Exercise Life | Weighted Average Exercise Price | Number Exercisable | Weighted Average Price |
| 0.01 | 184,225 | 9.0 | \$ 0.01 | 184,225 | \$ 0.01 |
| 0.47 | 919,437 | 6.7 | 0.47 | 692,331 | 0.47 |
| 0.68 | 6,629,877 | 9.4 | 0.68 | 2,636,662 | 0.68 |
| 0.75 | 50,000 | 9.9 | 0.75 | — | — |
| 4.65 | 25,000 | 7.1 | 4.65 | 25,000 | 4.65 |
| | 7,808,539 | 9.1 | \$ 0.65 | 3,538,218 | \$ 0.63 |

Targacept, Inc.
Notes to Financial Statements—(continued)

12. Equity Incentive Plan (continued)

A summary of options outstanding as of September 30, 2004 (unaudited) is as follows:

| Exercise Price | Options Outstanding | | | Options Exercisable | |
|----------------|---------------------|--|---------------------------------|---------------------|------------------------|
| | Number Outstanding | Weighted Average Remaining Contractual Exercise Life | Weighted Average Exercise Price | Number Exercisable | Weighted Average Price |
| 0.01 | 209,225 | 8.4 | \$ 0.01 | 184,225 | \$ 0.01 |
| 0.47 | 702,078 | 6.0 | 0.47 | 698,423 | 0.47 |
| 0.68 | 6,050,382 | 8.7 | 0.68 | 2,957,955 | 0.68 |
| 0.75 | 388,626 | 9.3 | 0.75 | 277,700 | 0.75 |
| | <u>7,350,311</u> | <u>8.5</u> | <u>\$ 0.64</u> | <u>4,118,303</u> | <u>\$ 0.62</u> |

During 2001, the Company granted 25,000 options above fair value at a weighted-average exercise price of \$4.65. The options had a weighted-average fair value of \$0. During 2002 and 2003, respectively, the Company granted 130,000 and 97,500 options below fair value at an exercise price of \$0.01 and fair value of \$0.67 per share. The fair value of these shares was recorded as compensation expense in the amounts \$129,710 and \$65,325, during 2002 and 2003, respectively. During the nine months ended September 30, 2004, the Company granted 25,000 options below fair value at an exercise price of \$0.01 and a fair value of \$0.74 per share. The fair value of these shares was recorded as compensation expense in the amount of approximately \$33,000.

See Note 18—Subsequent Events.

13. Leases

Prior to March 1, 2002, the Company leased its office space and certain equipment under a non-cancelable, one-year operating lease agreement with RJRT. Rent expense incurred by the Company under the RJRT lease was approximately \$609,000 and \$106,000 for the years ended December 31, 2001 and 2002, respectively. The Company has no future minimum lease payments to RJRT as of December 31, 2003.

On March 1, 2002, the Company entered into an agreement with Wake Forest University to lease an office and research facility in Winston-Salem, North Carolina with an initial term that extends through July 31, 2007. The lease contains a renewal option for up to one additional five-year term, with a lease rate similar to the original agreement. Rent expense incurred by the Company under this lease was approximately \$904,000, \$1,456,000 and \$1,092,000 for the years ended December 31, 2002, 2003 and the nine months ended September 30, 2004, respectively. Rent expense is offset by the monthly recognition of the deferred rent incentive discussed in Note 2. At December 31, 2003, the Company has the following future minimum lease payments in relation to this lease:

| | |
|---------------------|---------------------|
| 2004 | \$ 1,455,552 |
| 2005 | 1,455,552 |
| 2006 | 1,455,552 |
| 2007 | 849,072 |
| 2008 and thereafter | — |
| | <u>\$ 5,215,728</u> |

Targacept, Inc.
Notes to Financial Statements—(continued)

14. Retirement Savings Plan

The Company has a 401(k) retirement plan that covers substantially all of its employees. This plan provides for the Company to make 100% matching contributions up to a maximum of 6% of employees' eligible compensation. The Company contributed \$171,000, \$290,000, \$298,000 and \$290,000 to the plan for the years ended December 31, 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively.

15. Collaborative Research and License Agreements

Aventis Pharma

In December 1998, the Company entered into a collaborative research and license agreement with Aventis Pharma ("Aventis") whereby the Company and Aventis agreed to collaborate on the discovery, development and commercialization of nicotinic agonists for use in prevention of certain human diseases. Under the agreement, as restated in January 2002, Aventis was granted a license under certain patent rights and knowledge to develop, manufacture and commercialize certain compounds. The agreement provides for the payment of research fees on a "fee for service" basis for development work that the Company agreed to perform. For the years ended December 31, 2001, 2002, and 2003 and the nine months ended September 30, 2004, these fees were \$1,100,000, \$1,389,000, \$1,303,000 and \$209,000, respectively. The Company is entitled to receive milestone payments under the contract at specified dates during the development period. The Company did not receive milestone payments under the agreement during 2001, 2002, 2003 or the nine months ended September 30, 2004. In addition, Aventis agreed to make royalty payments based on net sales of products developed and sold. In general, either party may terminate the agreement in the event of a material breach by the other party, including a material breach of research obligations or the issuance of third-party patent rights to a competitor. Additionally, Aventis may terminate the agreement without cause by providing the Company with 30 days, written notice at any time after the research term, in which case all rights to the product candidate would revert to the Company. All royalty and other payment obligations of the parties survive any termination of the agreement.

During 1999, the Company received a one-time non-refundable license fee payment of \$2,000,000 to enter into this agreement. The product candidate subject to the agreement has not completed the research and clinical development process. Accordingly, the Company has deferred recognition of the license fee and is amortizing it over the expected term of the research and development period. The Company recognized \$250,000, \$250,000, \$100,000 and \$75,000 of the license fee payment during 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively.

On January 21, 2002, the Company entered into a second collaborative research and license agreement with Aventis to discover and develop drugs, derived from the Aventis library of compounds for the treatment of Alzheimer's disease and other disorders of the central nervous system. The second agreement was structured similarly to the first agreement. The research terms of the agreement will extend for two years.

See Note 18—Subsequent Events.

Dr. Falk Pharma

On January 26, 2001, the Company entered into a collaborative research development and license agreement with Dr. Falk Pharma GmbH ("Dr. Falk Pharma"), a German corporation, pursuant to which the parties agreed to collaborate to research, develop and commercialize nicotinic therapeutics for use in the prevention or treatment of ulcerative colitis and other gastrointestinal and liver diseases. Upon execution of the agreement, Dr. Falk Pharma paid the Company a \$1,000,000 license fee and purchased 111,111 shares of the Company's common stock for \$1,000,000. The Company is continuing to advance the compound subject to the agreement through the research and clinical development process. Therefore, the Company has deferred recognition of the license fee payment and is amortizing it over the expected term of the research and development period. To account for the

Targacept, Inc.**Notes to Financial Statements—(continued)****15. Collaborative Research and License Agreements (continued)**

\$1,000,000 in proceeds for the common stock, the Company used the estimated fair value of the common stock to value the shares issued to arrive at a total equity value of \$75,556, with the remaining proceeds of \$924,494 allocated to deferred revenue. This deferred revenue is also being amortized over the expected term of the research and development period. The Company recognized \$353,000, \$385,000, \$170,000 and \$127,000 of deferred revenue under this agreement during 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively. As of September 30, 2004, deferred revenue under this agreement was approximately \$890,000 and was included in deferred license fee revenue in the accompanying balance sheet.

Dr. Falk Pharma agreed to make royalty payments based on net profits from products containing compounds developed under the agreement. For the years ended December 31, 2001, 2002, 2003 and the nine months ended September 30, 2004, the Company did not pay or receive any royalties related to this agreement.

16. Acquisition of Inversine Product

On August 5, 2002, the Company purchased from Layton Bioscience the Inversine product line, inventory and related patent rights for cash consideration of \$3,500,000. The purchase was made in order to further the Company's science and portfolio of compounds, and to further the Company's development in certain neuropsychiatric indications.

This transaction was accounted for as an acquisition of assets. The aggregate purchase price was allocated to the assets acquired based on their fair values as follows:

| | <u>Amount</u> |
|-------------------------------------|---------------|
| Inventories | \$ 192,000 |
| Intangible assets acquired: | |
| Core technology | 296,000 |
| Developed product technology | 346,000 |
| In-process research and development | 2,666,000 |
| | <hr/> |
| Aggregate purchase price | \$ 3,500,000 |
| | <hr/> |

In determining the total consideration as well as the allocation of the purchase price including the amount of in-process research and development, the Company considered as part of its analysis an appraisal prepared by an independent appraiser that used established valuation techniques appropriate for the pharmaceutical industry. The amount allocated to in-process research and development was expensed upon acquisition. A one-time charge of \$2,666,000 for purchased in-process research and development arising from the acquisition has been reflected in the Statement of Operations for the year ended December 31, 2002.

17. Related Party Transactions

RJRT is the holder of 5,000,000 shares of Series A redeemable preferred stock convertible to 5,000,000 shares of common stock, a warrant to purchase 1,612,903 shares of common stock, and options to purchase 31,725 shares of common stock. The Company has entered into the following transactions and agreements with RJRT in the ordinary course of business.

During 2002, the Company entered into an agreement to borrow \$2,500,000 from RJRT accruing interest at 6.6%. The note is repayable in monthly installments of \$59,000 through the maturity date of May 1, 2006, and is secured by equipment owned by us with a book value of approximately \$2,373,000, net of accumulated

Targacept, Inc.
Notes to Financial Statements—(continued)

17. Related Party Transactions (continued)

depreciation, at December 31, 2003. In January 2004, the Company amended the note agreement with RJRT to allow for up to three additional tranches to be advanced to the Company for up to a total of \$2,000,000. Each of the additional tranches will accrue interest at the 4-year U.S. Treasury rate plus 3.5% determined as at the day the additional tranche is advanced and will be repayable in 48 equal monthly installments. The Company was advanced an additional tranche on April 1, 2004 in the amount of \$1,027,000. This additional tranche accrues interest at 5.87% and is repayable in monthly payments of \$24,000 through the maturity date of April 1, 2008. Under this related party note payable, the Company paid RJRT \$416,000, \$772,000 and \$596,000 during 2002, 2003 and the nine months ended September 30, 2004, respectively.

Prior to March 1, 2002, the Company leased office space and certain equipment under a non-cancelable operating lease agreement with RJRT. Rent expense incurred by the Company under the RJRT lease was approximately \$609,000 and \$106,000 for the years ended December 31, 2001 and 2002, respectively. The Company has no future minimum lease payments to RJRT as of December 31, 2003.

A member of the Company's board of directors serves as an officer of RJRT. Equity compensation for such director's service has been made, at the director's request, directly to RJRT. The numbers of shares subject to stock options granted to RJRT during the years ended December 31, 2001, 2002 and 2003 and the nine months ended September 30, 2004 in connection with the director's services are 0, 32,500, 7,500 and 0, respectively. In addition, a stock option for an additional 32,500 shares was granted to RJRT during the year ended December 31, 2002 in connection with the services of a former director. A portion of that option, representing 15,775 shares, was forfeited when that director ceased to serve as a director. In connection with the issuance of the stock options, the Company recognized compensation expense of \$0, \$43,550, \$2,512 and \$2,512 during 2001, 2002, 2003 and the nine months ended September 30, 2004, respectively.

Prior to December 31, 2003, the Company used the services of a RJRT employee for toxicology studies and purchased materials used for research and development and copy and print services through RJRT. The Company paid RJRT \$810,000, \$525,000 and \$201,000 for these services during 2001, 2002, and 2003, respectively.

See Note 18—Subsequent Events.

18. Subsequent Events

On December 3, 2004, Aventis provided the Company with 30 days advance written notice of Aventis' plans to terminate the collaborative research and license agreement between the companies entered into in December 1998 and restated in January 2002 (see Note 15). The termination of the agreement was effective on January 2, 2005 and was within the provisions of termination clauses of the agreement. As a result of the termination of the agreement, the Company will recognize the remaining deferred revenue of \$825,000 related to the agreement during the fourth quarter of 2004.

On December 6, 2004, the Company completed a private placement of 27,272,728 shares of Series C and received cash of approximately \$32,900,000, net of offering costs. The terms of the issuance are consistent with those of the previous Series C issuances as discussed in Note 9. Pursuant to EITF Issue No. 98-5, Accounting for Convertible Securities with Beneficial Conversion Features, and EITF 00-27, Application of Issue No. 98-5 to Certain Convertible Instruments, the Company will record a non-cash preferred stock charge at the date of issuance by offsetting charges and credits to additional paid-in-capital of \$, which is the difference in the conversion price of the Series C shares issued on December 6, 2004 and the underlying value of the conversion shares.

On December 6, 2004, the Company amended its certificate of incorporation to, among other things, increase the authorized shares of common stock to 125,000,000 and to reduce the public offering price per share that would trigger automatic conversion of the redeemable convertible preferred stock from \$3.60 to \$2.15.

Targacept, Inc.

Notes to Financial Statements—(continued)

18. Subsequent Events (continued)

On December 15, 2004, the Company entered into a development agreement with The Stanley Medical Research Institute (“SMRI”). In connection with the agreement, SMRI paid the Company \$1,250,000 in return for the issuance by the Company of a convertible promissory note in an equal principal amount. The note bears interest at 10% per annum and matures on January 1, 2007. However, if not earlier paid, the outstanding principal and accrued interest under the note will automatically convert into shares of the Company’s common stock concurrently with the completion of the Company’s initial public offering at a conversion price equal to the initial public offering price. The Company is entitled to receive milestone payments under the agreement upon the achievement of specified milestones during the development period. The Company is required to make royalty payments based on net sales of products developed and sold.

On December 23, 2004, the Company was advanced an additional tranche under the note agreement with RJRT in the amount of \$973,000. This additional tranche accrues interest at 6.89% and is repayable in monthly installments of \$23,000 through the maturity date of January 1, 2009.

On _____, 2005 the Company’s Board of Directors adopted, and on _____, 2005 the stockholders approved, a _____ to _____ reverse stock split of the Company’s common stock effective as of _____. All common stock and per common share amounts for all periods presented in the accompanying financial statements have been restated to reflect the effect of this common stock split.

Targacept, Inc.
Notes to Financial Statements—(continued)

19. Selected Quarterly Financial Data (Unaudited)

| | 2002 Quarter | | | |
|---|--------------|-------------|-------------|-------------|
| | First | Second | Third | Fourth |
| Net revenue | \$ 489,891 | \$ 412,339 | \$ 471,219 | \$ 912,909 |
| Gross profit (loss) on product sales | — | — | — | (857) |
| Operating loss | (4,335,806) | (3,537,219) | (8,250,014) | (4,879,471) |
| Net loss | (4,421,557) | (3,510,492) | (8,250,530) | (4,889,127) |
| Net loss attributable to common stockholders | (5,373,554) | (4,462,489) | (9,202,527) | (6,206,681) |
| Basic and diluted net loss per share attributable to common stockholders(1) | \$ (10.83) | \$ (8.38) | \$ (15.81) | \$ (10.05) |
| Weighted average common shares outstanding—basic and diluted | 496,382 | 532,673 | 581,894 | 617,423 |
| | 2003 Quarter | | | |
| | First | Second | Third | Fourth |
| Net revenue | \$ 690,796 | \$ 526,517 | \$ 598,840 | \$ 642,132 |
| Gross profit (loss) on product sales | 111,509 | (67,923) | (957) | 29,154 |
| Operating loss | (4,275,065) | (5,997,799) | (4,525,572) | (5,265,435) |
| Net loss | (4,185,042) | (5,775,002) | (4,387,882) | (5,047,395) |
| Net loss attributable to common stockholders | (6,100,000) | (7,916,891) | (6,529,771) | (7,189,287) |
| Basic and diluted net loss per share attributable to common stockholders(1) | \$ (9.48) | \$ (10.99) | \$ (7.15) | \$ (7.26) |
| Weighted average common shares outstanding—basic and diluted | 643,571 | 720,093 | 913,185 | 989,874 |
| | 2004 Quarter | | | |
| | First | Second | Third | |
| Net revenue | 496,939 | 528,026 | 555,583 | |
| Gross profit (loss) on product sales | 6,061 | 494,780 | 55,697 | |
| Operating loss | (6,843,593) | (6,437,455) | (6,711,932) | |
| Net loss | (6,637,935) | (6,433,767) | (6,665,238) | |
| Net loss attributable to common shareholders | (8,779,826) | (8,575,657) | (8,807,125) | |
| Basic and diluted net loss per share attributable to common stockholders(1) | (7.89) | (5.14) | (4.68) | |
| Weighted average common shares outstanding—basic and diluted | 1,112,591 | 1,668,778 | 1,880,325 | |

Diluted EPS is identical to Basic EPS since common stock equivalent shares are excluded from the calculation, as their effect is anti-dilutive.

(1) Per common share amounts for the quarters and full years have been calculated separately. Accordingly, quarterly amounts do not add to the annual amount because of differences in the weighted-average common shares outstanding during each period principally due to the effect of the Company's issuing shares of its common stock during the year.

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You should rely only on the information contained in this prospectus. We have not authorized anyone to provide information different from that contained in this prospectus. We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of our common stock.

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Until _____, 2005 (25 days after the date of this prospectus), all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to the dealer's obligation to deliver a prospectus when acting as an underwriter and with respect to unsold allotments or subscriptions.



Shares

Common Stock

Deutsche Bank Securities

Pacific Growth Equities, LLC

CIBC World Markets

Lazard

Prospectus

, 2005

Part II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution.

The following table sets forth the expenses in connection with the offering, all of which will be borne by us. All amounts shown are estimates except for the Securities and Exchange Commission registration fee, the NASDAQ National Market listing fee and the NASD filing fee.

| | |
|---|-------------|
| Securities and Exchange Commission registration fee | \$ 10,928 |
| NASDAQ National Market listing fee | 100,000 |
| NASD filing fee | 9,125 |
| Blue sky fees and expenses | * |
| Accounting fees and expenses | * |
| Legal fees and expenses | * |
| Transfer agent and registrar fees and expenses | * |
| Printing and engraving expenses | * |
| Miscellaneous | * |
| Total | \$ * |

* To be filed by amendment.

Item 14. Indemnification of Directors and Officers.

Our Third Amended and Restated Certificate of Incorporation, as amended and in effect as of the date of this registration statement, and our Fourth Amended and Restated Certificate of Incorporation to be in effect upon completion of this offering (as may be in effect from time to time, the "Certificate") provide that, except to the extent prohibited by the Delaware General Corporation Law, as amended (the "DGCL"), our directors shall not be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duty while serving as our directors. Under the DGCL, our directors have a fiduciary duty to us that is not eliminated by this provision of the Certificate and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available. In addition, each director will continue to be subject to liability under the DGCL for breach of the director's duty of loyalty to us or our stockholders, for acts or omissions that are found by a court of competent jurisdiction to be not in good faith or involving intentional misconduct, for knowing violations of law, for actions leading to improper personal benefit to the director and for payment of dividends or approval of stock repurchases or redemptions that are prohibited by the DGCL. This provision also does not affect our directors' responsibilities under any other laws, such as federal securities laws or state or federal environmental laws.

Section 145 of the DGCL empowers a corporation to indemnify its directors and officers against expenses (including attorneys' fees), judgments, fines and amounts paid in settlements actually and reasonably incurred by them in connection with any action, suit or proceeding brought by third parties by reason of the fact that they were or are directors or officers of the corporation, if they acted in good faith, in a manner they reasonably believed to be in or not opposed to the best interests of the corporation and, with respect to any criminal action or proceeding, had no reason to believe that their conduct was unlawful. The DGCL provides further that the indemnification permitted thereunder shall not be deemed exclusive of any other rights to which the directors and officers may be entitled under the corporation's bylaws, any agreement, a vote of stockholders or otherwise. The Certificate provides that, to the fullest extent permitted by Section 145 of the DGCL, we shall indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding (whether civil, criminal, administrative or investigative) by reason of the fact that such person is or was a director or officer of us, or is or was serving at our request as a director, officer or trustee of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise, against expenses

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(including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding. At present, there is no pending litigation or proceeding involving any director or officer as to which indemnification will be required or permitted under the Certificate and we are not aware of any threatened litigation or proceeding that may result in a claim for such indemnification.

Section 145 of the DGCL also empowers a corporation to purchase insurance for its officers and directors for such liabilities. We maintain liability insurance for our officers and directors.

Item 15. Recent Sales of Unregistered Securities.

Set forth below is information regarding shares of common stock and preferred stock issued, and options and warrants granted, by us since August 22, 2000. Also included is the consideration, if any, received by us for such shares, options and warrants and information relating to the section of the Securities Act, or rule of the Securities and Exchange Commission, under which exemption from registration was claimed.

(a) Issuance of Securities

1. On August 22, 2000, at the time that we became an independent company, we issued an aggregate of 309,424 shares of our common stock at a purchase price per share of \$0.001 to each of Dr. deBethizy, Dr. Bencherif, Dr. Caldwell and Dr. Patrick M. Lippiello for an aggregate purchase price of approximately \$309.

2. On August 22, 2000, we recapitalized our 500 outstanding shares of common stock held by R.J. Reynolds Tobacco Company, our then parent corporation, into 5,000,000 shares of series A convertible preferred stock and a warrant to purchase 1,612,903 shares of common stock at an exercise price of \$4.65 per share. All of the shares of series A convertible preferred stock and the warrant were issued to R.J. Reynolds Tobacco Company, which subsequently assigned them to R.J. Reynolds Tobacco Holdings, Inc. As a result of price protection provisions contained in the warrant, the exercise price was reduced to \$1.95 per share upon our issuance of shares of series C convertible preferred stock in November 2002 and March 2003. Each share of series A convertible preferred stock will convert into one share of common stock concurrently with the completion of this offering.

3. On August 22, 2000, we issued and sold an aggregate of 5,892,473 shares of our series B convertible preferred stock at a purchase price per share of \$4.65 to investors affiliated with EuclidSR Partners, L.P., Burrill & Company LLC, Societe Generale Asset Management Finance (which subsequently assigned its shares to FCPR SGAM Biotechnology Fund), Genavent Venture Fund, Auriga Ventures, Advent Private Equity Fund II, FCPR CDC-Innovation 2000 and Longleaf Venture Fund, LLC (now known as Academy Venture Fund, LLC) for an aggregate purchase price of approximately \$27.4 million. These shares will convert into common stock at the rate of approximately 2.38 shares of common stock for each share of series B convertible preferred stock concurrently with the completion of this offering.

4. On November 30, December 5 and December 19, 2000, we issued and sold an aggregate of 645,161 shares of our series B convertible preferred stock at a purchase price per share of \$4.65 to investors affiliated with EuclidSR Partners, L.P. and Longleaf Venture Fund, LLC (now known as Academy Venture Fund, LLC) for an aggregate purchase price of approximately \$3.0 million. These shares will convert into common stock at the rate of approximately 2.38 shares of common stock for each share of series B convertible preferred stock concurrently with the completion of this offering.

5. On January 26, 2001, we issued and sold an aggregate of 29,933 shares of our series B convertible preferred stock, valued at \$4.65 per share, to Andre L. Lamotte, Joseph F. Lovett and Jeffrey D. Wager in partial satisfaction of amounts payable by us for consulting services rendered. The aggregate amount of consideration was approximately \$139,000. These shares will convert into common stock at the rate of one share of common stock for each share of series B convertible preferred stock concurrently with the completion of this offering.

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6. On January 30, 2001, we issued and sold an aggregate of 111,111 shares of our common stock at a purchase price of \$9.00 per share to Dr. Falk Pharma GmbH, our collaborative partner, for an aggregate purchase price of approximately \$1.0 million.

7. On August 8, 2002, June 11, 2003 and October 15, 2004, we issued and sold an aggregate of 72,500 shares of restricted stock to Mr. Skaletsky for an aggregate purchase price of \$725.

8. On November 26, 2002, we issued and sold an aggregate of 37,764,180 shares of our series C convertible preferred stock at a purchase price per share of \$1.21 to investors affiliated with Nomura International plc, New Enterprise Associates 10, Limited Partnership, CDIB Bioscience Ventures I, Inc., Easton Hunt Capital Partners, L.P., EuclidSR Partners, L.P., Burrill & Company LLC, Genavent Fund, FCPR SGAM AI Biotechnology Fund, Auriga Ventures, FCPR CDC-Innovation 2000, Advent Private Equity Fund II and Academy Venture Fund, LLC for an aggregate purchase price of approximately \$45.7 million. These shares will convert into common stock at the rate of approximately 1.08 shares of common stock for each share of series C convertible preferred stock concurrently with the completion of this offering.

9. On March 14, 2003, we issued and sold an aggregate of 11,404,958 shares of our series C convertible preferred stock at a purchase price per share of \$1.21 to investors affiliated with JAFCO G-9(A) Venture Capital Investment Limited Partnership, Rock Castle Ventures, Cogene Biotech Ventures Five, Bison Capital, LLC and Oxford Bioscience Partners IV L.P. for an aggregate purchase price of approximately \$13.8 million. These shares will convert into common stock at the rate of approximately 1.08 shares of common stock for each share of series C convertible preferred stock concurrently with the completion of this offering.

10. On April 18, 2003, we issued and sold an aggregate of 25,000 shares of restricted stock to Mr. Richard for an aggregate purchase price of \$250.

11. On December 6, 2004, we issued and sold an aggregate of 27,272,728 shares of our series C convertible preferred stock at a purchase price per share of \$1.21 to New Enterprise Associates 10, Limited Partnership, EuclidSR Partners, L.P., Burrill Biotechnology Capital Fund, L.P., R.J. Reynolds Tobacco Holdings, Inc., Nomura Phase4Ventures LP and investors affiliated with CDIB Bioscience Ventures I, Inc., Genavent Fund, FCPR SGAM AI Biotechnology Fund, FCPR CDC-Innovation 2000, Advent Private Equity Fund II and JAFCO G-9(A) Venture Capital Investment Limited Partnership for an aggregate purchase price of approximately \$33.0 million. These shares will convert into common stock at the rate of approximately 1.08 shares of common stock for each share of series C convertible preferred stock concurrently with the completion of this offering.

12. On December 15, 2004, we issued a \$1.25 million convertible promissory note to The Stanley Medical Research Institute. The note bears interest at 10% per annum and matures on January 1, 2007. However, if not earlier paid, the outstanding principal and accrued interest under the note will automatically convert into shares of our common stock concurrently with the completion of this offering at a conversion price equal to the initial public offering price.

13. Since inception to December 31, 2004, we have granted:

- options to purchase an aggregate of 8,694,419 shares of common stock at exercise prices ranging from \$0.01 to \$4.65 per share under our 2000 Equity Incentive Plan, as amended, with a weighted average exercise price of \$0.66 per share, to employees, directors and individual consultants;
- restricted stock awards for an aggregate of 97,500 shares of common stock at a purchase price of \$0.01 per share under our 2000 Equity Incentive Plan, as amended; and
- options to purchase an aggregate of 255,000 shares of common stock at an exercise price of \$0.01 per share to non-individual consultants under our 2000 Equity Incentive Plan, as amended.

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The weighted average exercise price of all options to purchase shares of common stock granted since inception and outstanding on December 31, 2004 is \$0.65 per share. As of December 31, 2004, there were 55 holders of record of shares of our common stock.

(b) No underwriters were involved in the foregoing sales of securities. The securities described in paragraphs (a)(1)—(12) of this Item 15 were issued to a combination of foreign and U.S. investors in reliance upon the exemption from the registration requirements of the Securities Act, as set forth in Sections 3(a)(9) or 4(2) under the Securities Act and Rule 506 of Regulation D promulgated thereunder relative to sales by an issuer not involving any public offering, or in reliance upon Regulation S promulgated under the Securities Act, to the extent an exemption from such registration was required. All purchasers of shares of our convertible preferred stock described in paragraph (a)(1)—(12) of this Item 15 represented to us in connection with their purchase that they were accredited investors and were acquiring the shares for investment and not distribution, that they could bear the risks of the investment and could hold the securities for an indefinite period of time. The purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration or an available exemption from such registration.

All of the foregoing securities are deemed restricted securities for purposes of the Securities Act. All certificates representing the issued shares of common stock described in this Item 15 included appropriate legends setting forth that the securities had not been registered and the applicable restrictions on transfer.

The issuance of stock options and the common stock issuable upon the exercise of such options as described in paragraph (a)(13) of this Item 15 were issued pursuant to written compensatory benefit plans or arrangements with our employees, directors and consultants, in reliance on the exemption provided by Rule 701 promulgated under the Securities Act. All recipients either received adequate information about us or had access, through employment or other relationships, to such information.

Item 16. Exhibits and Financial Statement Schedules.

(a) Exhibits.

| <u>Exhibit No.</u> | <u>Description</u> |
|--------------------|---|
| 1.1* | Form of Underwriting Agreement. |
| 3.1(a)#** | Third Amended and Restated Certificate of Incorporation of the Company. |
| 3.1(b)* | Form of Fourth Amended and Restated Certificate of Incorporation of the Company, to be effective upon completion of this offering. |
| 3.2(a)** | Amended and Restated Bylaws of the Company. |
| 3.2(b)* | Form of Bylaws of the Company, to be effective upon completion of this offering. |
| 4.1* | Specimen common stock certificate. |
| 4.2(a) | Third Amended and Restated Investor Rights Agreement, dated May 12, 2004, by and among the Company and certain stockholders of the Company. |
| 4.2(b) | Amendment No. 1 dated December 6, 2004 to Third Amended and Restated Investor Rights Agreement dated May 12, 2004. |
| 4.3** | Warrant to Purchase Common Stock, dated August 22, 2000, granted to R.J. Reynolds Tobacco Company and subsequently assigned to R.J. Reynolds Tobacco Holdings, Inc. |
| 4.4** | Convertible Promissory Note of the Company in favor of The Stanley Medical Research Institute dated December 15, 2004. |
| 5.1* | Opinion of Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. |
| 5.2* | Opinion of Womble Carlyle Sandridge & Rice, PLLC. |

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| <u>Exhibit No.</u> | <u>Description</u> |
|--------------------|--|
| 10.1* | Form of Indemnification Agreement between the Company and each of its directors and officers. |
| 10.2(a)** | Lease Agreement, dated as of August 1, 2002, by and between the Company and Wake Forest University Health Sciences. |
| 10.2(b) | First Lease Amendment to Lease Agreement, dated as of August 1, 2002, by and between the Company and Wake Forest University Health Sciences. |
| 10.3** | Loan Agreement, dated as of April 19, 2002, between the Company and the City of Winston-Salem. |
| 10.4** | Amended and Restated Note and Security Agreement, dated January 30, 2004, issued by the Company in favor of R.J. Reynolds Tobacco Holdings, Inc. |
| 10.5** | Targacept, Inc. 2000 Equity Incentive Plan, as amended. |
| 10.6* | Targacept, Inc. 2005 Stock Incentive Plan. |
| 10.7** | Employment Agreement, dated as of August 22, 2000, by and between the Company and J. Donald deBethizy. |
| 10.8** | Employment Agreement, dated as of August 22, 2000, by and between the Company and Merouane Bencherif. |
| 10.9** | Employment Agreement, dated as of August 22, 2000, by and between the Company and William S. Caldwell. |
| 10.10** | Employment Agreement, dated as of April 24, 2001, by and between the Company and Geoffrey Dunbar. |
| 10.11** | Employment Agreement, dated as of February 8, 2002, by and between the Company and Alan Musso. |
| 10.12** | Employment Agreement, dated as of September 1, 2003, by and between the Company and Jeffrey P. Brennan. |
| 10.13(a)** | Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |
| 10.13(b)** | Amended and Restated Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |
| 10.13(c)** | Letter Agreement, dated March 18, 2003, amending the Amended and Restated Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA and the Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |
| 10.14** | Collaborative Research, Development and License Agreement, dated as of January 26, 2001, by and between the Company and Dr. Falk Pharma GmbH. |
| 10.15** | Asset Purchase Agreement, dated as of June 28, 2002, by and between the Company and Layton Bioscience, Inc. |
| 10.16** | Asset Purchase and Trademark Assignment Agreement, dated March 19, 1998, by and between the Company (as assignee of Layton Bioscience, Inc.) and Merck & Co., Inc. |
| 10.17** | Amended and Restated License Agreement, dated as of March 9, 2004, by and between the Company and the University of South Florida Research Foundation, Inc. |
| 10.18(a)** | License Agreement, dated October 6, 1997, by and between the Company (as assignee of R.J. Reynolds Tobacco Company) and Virginia Commonwealth University Intellectual Property Foundation. |
| 10.18(b)** | Amendment to License Agreement, dated February 11, 2004, to the License Agreement, dated October 6, 1997, by and between the Company (as assignee of R.J. Reynolds Tobacco Company) and Virginia Commonwealth University Intellectual Property Foundation. |

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| <u>Exhibit No.</u> | <u>Description</u> |
|--------------------|---|
| 10.19+** | License Agreement, dated as of July 9, 2002, by and between the Company and the Medical College of Georgia Research Institute, Inc. |
| 10.20+** | License Agreement, dated May 26, 1999, by and between the Company and the University of Kentucky Research Foundation. |
| 10.21+** | License Agreement, dated as of August 12, 2002, between the Company and Wake Forest University Health Sciences. |
| 10.22+** | Development and Production Agreement for Active Pharmaceutical Ingredients, dated as of February 1, 2004, by and between the Company and Siegfried Ltd. |
| 10.23+*** | Development Agreement, dated as of December 15, 2004, by and between the Company and The Stanley Medical Research Institute. |
| 23.1 | Consent of Ernst & Young LLP. |
| 23.2* | Consent of Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. (included in Exhibit 5.1). |
| 23.3* | Consent of Womble Carlyle Sandridge & Rice, PLLC (included in Exhibit 5.2). |
| 24.1** | Power of Attorney (included on signature page). |

* To be filed by amendment.

** Previously filed.

Replaces Exhibit 3.1(a) filed with the Company's Registration Statement on Form S-1 dated May 14, 2004.

+ Confidential treatment has been granted with respect to certain portions of this Exhibit, which portions have been omitted and filed separately with the Securities and Exchange Commission as part of an application for confidential treatment pursuant to the Securities Act of 1933, as amended.

++ Portions of this Exhibit have been omitted and filed separately with the Securities and Exchange Commission as part of an application for confidential treatment pursuant to the Securities Act of 1933, as amended.

(b) Financial Statement Schedules.

All information for which provision is made in the applicable accounting regulations of the Securities and Exchange Commission is either included in the financial statements or is not required under the related instructions or is inapplicable, and therefore has been omitted.

Item 17. Undertakings.

The undersigned registrant hereby undertakes to provide to the underwriters at the closing specified in the underwriting agreement, certificates in such denominations and registered in such names as required by the underwriters to permit prompt delivery to each purchaser.

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the provisions described herein, or otherwise, the registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as a part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant has duly caused this Amendment No. 4 to the registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Winston-Salem, State of North Carolina, on January 20, 2005.

TARGACEPT, INC.

/s/ J. DONALD DEBETHIZY

By: _____
J. Donald deBethizy
Chief Executive Officer and President

Pursuant to the requirements of the Securities Act of 1933, this Amendment No. 4 to the registration statement has been signed by the following persons in the capacities indicated on January 20, 2005.

/s/ J. DONALD DEBETHIZY

Name: J. Donald deBethizy
Title: Chief Executive Officer, President and Director
(Principal Executive Officer)

*

Name: Mark Skaletsky
Title: Chairman of the Board of Directors

*

Name: Charles A. Blixt
Title: Director

*

Name: Errol B. De Souza
Title: Director

*

Name: John P. Richard
Title: Director

/s/ ALAN A. MUSSO

Name: Alan A. Musso
Title: Vice President and Chief Financial Officer
(Principal Financial Officer and Principal
Accounting Officer)

*

Name: M. James Barrett
Title: Director

*

Name: G. Steven Burrill
Title: Director

*

Name: Elaine V. Jones
Title: Director

*

Name: Alan G. Walton
Title: Director

*By: /s/ J. DONALD DEBETHIZY

J. Donald deBethizy
Attorney-in-fact

EXHIBIT INDEX

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| 4.1* | Specimen common stock certificate. |
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| 10.6* | Targacept, Inc. 2005 Stock Incentive Plan. |
| 10.7** | Employment Agreement, dated as of August 22, 2000, by and between the Company and J. Donald deBethizy. |
| 10.8** | Employment Agreement, dated as of August 22, 2000, by and between the Company and Merouane Bencherif. |
| 10.9** | Employment Agreement, dated as of August 22, 2000, by and between the Company and William S. Caldwell. |
| 10.10** | Employment Agreement, dated as of April 24, 2001, by and between the Company and Geoffrey Dunbar. |
| 10.11** | Employment Agreement, dated as of February 8, 2002, by and between the Company and Alan Musso. |
| 10.12** | Employment Agreement, dated as of September 1, 2003, by and between the Company and Jeffrey P. Brennan. |
| 10.13(a)+** | Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |
| 10.13(b)+** | Amended and Restated Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |

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| <u>Exhibit No.</u> | <u>Description</u> |
|--------------------|--|
| 10.13(c)** | Letter Agreement, dated March 18, 2003, amending the Amended and Restated Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA and the Collaborative Research and License Agreement, dated as of January 21, 2002, by and between the Company and Aventis Pharma SA. |
| 10.14+** | Collaborative Research, Development and License Agreement, dated as of January 26, 2001, by and between the Company and Dr. Falk Pharma GmbH. |
| 10.15** | Asset Purchase Agreement, dated as of June 28, 2002, by and between the Company and Layton Bioscience, Inc. |
| 10.16+** | Asset Purchase and Trademark Assignment Agreement, dated March 19, 1998, by and between the Company (as assignee of Layton Bioscience, Inc.) and Merck & Co., Inc. |
| 10.17+** | Amended and Restated License Agreement, dated as of March 9, 2004, by and between the Company and the University of South Florida Research Foundation, Inc. |
| 10.18(a)+** | License Agreement, dated October 6, 1997, by and between the Company (as assignee of R.J. Reynolds Tobacco Company) and Virginia Commonwealth University Intellectual Property Foundation. |
| 10.18(b)+** | Amendment to License Agreement, dated February 11, 2004, to the License Agreement, dated October 6, 1997, by and between the Company (as assignee of R.J. Reynolds Tobacco Company) and Virginia Commonwealth University Intellectual Property Foundation. |
| 10.19+** | License Agreement, dated as of July 9, 2002, by and between the Company and the Medical College of Georgia Research Institute, Inc. |
| 10.20+** | License Agreement, dated May 26, 1999, by and between the Company and the University of Kentucky Research Foundation. |
| 10.21+** | License Agreement, dated as of August 12, 2002, between the Company and Wake Forest University Health Sciences. |
| 10.22+** | Development and Production Agreement for Active Pharmaceutical Ingredients, dated as of February 1, 2004, by and between the Company and Siegfried Ltd. |
| 10.23+++ | Development Agreement, dated as of December 15, 2004, by and between the Company and The Stanley Medical Research Institute. |
| 23.1 | Consent of Ernst & Young LLP. |
| 23.2* | Consent of Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. (included in Exhibit 5.1). |
| 23.3* | Consent of Womble Carlyle Sandridge & Rice, PLLC (included in Exhibit 5.2). |
| 24.1** | Power of Attorney (included on signature page). |

* To be filed by amendment.

** Previously filed.

Replaces Exhibit 3.1(a) filed with the Company's Registration Statement on Form S-1 dated May 14, 2004.

+ Confidential treatment has been granted with respect to certain portions of this Exhibit, which portions have been omitted and filed separately with the Securities and Exchange Commission as part of an application for confidential treatment pursuant to the Securities Act of 1933, as amended.

++ Portions of this Exhibit have been omitted and filed separately with the Securities and Exchange Commission as part of an application for confidential treatment pursuant to the Securities Act of 1933, as amended.

THIRD AMENDED AND RESTATED
INVESTOR RIGHTS AGREEMENT

THIS THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT (this “**Agreement**”) dated as of May 12, 2004, is by and among TARGACEPT, INC., a Delaware corporation (the “**Company**”), and the undersigned holders (the “**Series C Investors**”) of the Company’s Series C Convertible Preferred Stock, \$0.001 par value per share (the “**Series C Stock**”), the undersigned holder (the “**Series A Investor**”) of the Company’s Series A Convertible Preferred Stock, \$0.001 par value per share (the “**Series A Stock**”), and the undersigned holders (the “**Series B Investors**” and, together with the Series C Investors and the Series A Investor, the “**Investors**”) of the Company’s Series B Convertible Preferred Stock, \$0.001 par value per share (the “**Series B Stock**” and, together with the Series C Stock and Series A Stock, the “**Preferred Stock**”).

W I T N E S S E T H:

WHEREAS, the Company and the Investors are parties to the Second Amended and Restated Investor Rights Agreement dated November 26, 2002 (the “**Current Agreement**”), which amended, restated and superseded the Amended and Restated Investor Rights Agreement dated July 16, 2001 (the “**Original Agreement**”); and

WHEREAS, the Company is contemplating a registered offering of Common Stock to the general public that is to be (i) approved by a majority of the members of the Board of Directors of the Company (the “**Board**”), with such majority to include (A) two directors who shall have been designated by either the Series A Investor or the Series B Investors (including any director designated by a specific Series B Investor or by a group of Series B Investors), and (B) one director designated by the Series C Investors (including any director designated by a specific Series C Investor or by a group of Series C Investors), and (ii) effected pursuant to a registration statement filed with, and declared effective by, the Commission under the Act (the “**Initial Public Offering**”); and

WHEREAS, effective as of the date of, and conditional on, consummation of the Initial Public Offering (the “**Effective Date**”), the Company and the Investors wish to amend and fully restate the Current Agreement in its entirety as set forth herein;

NOW, THEREFORE, in consideration of the premises and the mutual terms and provisions hereof, the parties hereto hereby agree as follows:

1. Definitions. For purposes of this Agreement, the following terms shall have the following respective meanings:

(a) “**Act**” shall mean the Securities Act of 1933, as amended, or any similar federal statute enacted hereafter, and the rules and regulations of the Commission thereunder, all as shall be in effect from time to time.

(b) “**Commission**” shall mean the Securities and Exchange Commission or any other federal agency that administers the Act.

(c) “**Common Stock**” shall mean the Company’s common stock, \$0.001 par value per share.

(d) “**Eligibility Date**” shall mean 180 days following the Effective Date.

(e) “**Holder**” shall mean an Investor that holds Registrable Securities or any transferee of an Investor that holds Registrable Securities to which registration rights hereunder have been transferred pursuant to Section 2.12.

(f) The terms “**register**,” “**registered**” and “**registration**” refer to a registration effected by preparing and filing a registration statement in compliance with the Act and the declaration or ordering of effectiveness of such registration statement by the Commission.

(g) “**Registrable Securities**” shall mean Series A Registrable Securities, Series B Registrable Securities and Series C Registrable Securities, collectively.

(h) “**Series A Registrable Securities**” shall mean (i) shares of Common Stock issued or issuable upon conversion of the Series A Stock, (ii) shares of Common Stock issued or issuable upon exercise of the warrant issued by the Company as of August 22, 2000 to R.J. Reynolds Tobacco Company, a New Jersey corporation (“**RJRT**”), and subsequently transferred to R.J. Reynolds Tobacco Holdings, Inc., to purchase up to 1,612,903 shares of Common Stock (the “**Special Warrant**”), and (iii) shares of Common Stock issued upon any subdivision, combination or reclassification of the foregoing or issued as a stock dividend or other distribution with respect to the foregoing; provided, that Series A Registrable Securities shall cease to be Series A Registrable Securities if (A) a registration statement with respect to the sale thereof shall have been filed and declared effective under the Act, (B) they are sold pursuant to Rule 144 under the Act (or any successor provision) or become saleable pursuant to Rule 144(k) under the Act (or any successor provision), (C) with respect to any Holder’s Series A Registrable Securities, all of such Holder’s Series A Registrable Securities become saleable under Rule 144 without impact from the volume limitations of Rule 144(e) (or any successor provision), or (D) they are sold in a private transaction in which a Holder’s rights hereunder are not validly transferred.

(i) “**Series B Registrable Securities**” shall mean (i) shares of Common Stock issued or issuable upon conversion of the Series B Stock, and (ii) shares of Common Stock issued upon any subdivision, combination or reclassification of the foregoing or issued as a stock dividend or other distribution with respect to the foregoing; provided, that Series B Registrable Securities shall cease to be Series B Registrable Securities if (A) a registration statement with respect to the sale thereof shall have been filed and declared effective under the Act, (B) they are sold pursuant to Rule 144 under the Act (or any successor provision) or become saleable pursuant to Rule 144(k) under the Act (or any successor provision), (C) with respect to any Holder’s Series B Registrable Securities, all of such Holder’s Series B Registrable Securities become saleable under Rule 144 without impact from the volume limitations of Rule 144(e) (or

any successor provision), or (D) they are sold in a private transaction in which a Holder's rights hereunder are not validly transferred.

(j) "**Series C Registrable Securities**" shall mean (i) shares of Common Stock issued or issuable upon conversion of the Series C Stock, and (ii) shares of Common Stock issued upon any subdivision, combination or reclassification of the foregoing or issued as a stock dividend or other distribution with respect to the foregoing; provided, that Series C Registrable Securities shall cease to be Series C Registrable Securities if (A) a registration statement with respect to the sale thereof shall have been filed and declared effective under the Act, (B) they are sold pursuant to Rule 144 under the Act (or any successor provision) or become saleable pursuant to Rule 144(k) under the Act (or any successor provision), (C) with respect to any Holder's Series C Registrable Securities, all of such Holder's Series C Registrable Securities become saleable under Rule 144 without impact from the volume limitations of Rule 144(e) (or any successor provision), or (D) they are sold in a private transaction in which a Holder's rights hereunder are not validly transferred.

(k) "**1934 Act**" shall mean the Securities Exchange Act of 1934, as amended, or any similar federal statute enacted hereafter, and the rules and regulations of the Commission thereunder, all as shall be in effect from time to time.

2. Registration Rights.

2.1 Demand Registration.

(a) Subject to the other provisions of this Section 2.1, Section 2.8 and Section 2.9, if, at any time or from time to time following the Eligibility Date (but in no event within three months after the effective date of any registration of the Company's securities, other than registrations on Form S-4, Form S-8 or comparable or successor forms and other than registrations for the account of selling stockholders on Form S-3 or a comparable or successor form), the Company shall receive a written request (specifying that it is being made pursuant to this Section 2.1) from (i) Holders of at least a majority of the Series A Registrable Securities and Series B Registrable Securities, considered together, or (ii) Holders of Series C Registrable Securities that the Company file a registration statement under the Act covering the registration for offer and sale of at least thirty percent (30%) of, in the case of clause (i) above, all Series A Registrable Securities and Series B Registrable Securities, considered together, and at least thirty percent (30%) of, in the case of clause (ii) above, all Series C Registrable Securities, then the Company shall, within ten (10) business days notify in writing all other Holders of such request. Within twenty (20) calendar days after such notice has been sent by the Company, any other Holder of Series A Registrable Securities or Series B Registrable Securities, in the case of clause (i) above, and any other Holder of Series C Registrable Securities, in the case of clause (ii) above, may give written notice to the Company of its intent to include its Registrable Securities in the registration, which notice shall specify the number of Registrable Securities to be included. As soon as practicable after the expiration of such 20-day period, the Company shall use its best efforts to cause all Registrable Securities that Holders have requested be registered to be registered under the Act. The Holders

may, if they so desire, individually or collectively condition their request or participation on price or other market terms being available at the time of registration.

(b) Notwithstanding the provisions of Section 2.1(a) and Section 2.3, if the Board, in its good faith judgment, determines by written resolution that any registration of Registrable Securities should not be made or continued because it would materially and detrimentally interfere with any material financing, acquisition, corporate reorganization or merger or other similar transaction involving the Company or any of its subsidiaries or any registration that the Company has already taken definite and substantial steps toward effecting, or would otherwise be materially detrimental to the stockholders of the Company (a “**Valid Business Reason**”), the Company may postpone filing a registration statement request under Section 2.1(a) or 2.3 until such Valid Business Reason no longer exists, but in no event for more than 90 days or more than once in any twelve-month period, and, in the event a registration statement has been filed relating to a registration request under Section 2.1(a) or Section 2.3, if the Valid Business Reason has not resulted from actions taken by the Company, the Company may cause such registration statement to be withdrawn and its effectiveness terminated or may postpone amending or supplementing such registration statement; and the Company shall give written notice of its determination to postpone or withdraw a registration statement and of the fact that the Valid Business Reason for such postponement or withdrawal no longer exists, in each case, promptly after the occurrence thereof.

(c) Each Holder of Registrable Securities agrees that, upon receipt of any notice from the Company that the Company has determined to withdraw any registration statement pursuant to Section 2.1(b), such Holder will discontinue its disposition of Registrable Securities pursuant to such registration statement and, if so directed by the Company, will deliver to the Company (at the Company’s expense) all copies, other than permanent file copies, then in such Holder’s possession of the prospectus covering such Registrable Securities that was in effect at the time of receipt of such notice. If the Company shall have withdrawn or prematurely terminated a registration statement filed under Section 2.1(a) or Section 2.3, the Company shall not be considered to have effected an effective registration for the purposes of this Agreement until the Company shall have filed a new registration statement covering the Registrable Securities covered by the withdrawn registration statement and such registration statement shall have been declared effective and shall not have been withdrawn. If the Company shall give any notice of withdrawal or postponement of a registration statement, the Company shall, at such time as the Valid Business Reason that caused such withdrawal or postponement no longer exists (but in no event later than 90 days after the date of the postponement), use its best efforts to effect the registration under the Securities Act of the Registrable Securities covered by the withdrawn or postponed registration statement in accordance with this Section 2.1(c) (unless the Holders making the registration request shall have withdrawn such request, in which case the Company shall not be considered to have effected an effective registration for the purposes of this Agreement).

2.2 Piggyback Registration.

(a) Subject to Section 2.8, if at any time after the Effective Date the Company proposes to register any of its securities under the Act, either for its own

account or for the account of others, in connection with the public offering of such securities solely for cash, on a registration form that would also permit the registration of Registrable Securities, the Company shall, each such time, promptly give each Holder written notice of such proposal. Upon the written request of any Holder given within 20 days after receipt of such notice from the Company, the Company shall use its best efforts to cause to be included in such registration under the Act all the Registrable Securities that each such Holder has requested be registered.

(b) The Holders' rights to registration under this Section 2.2 are in addition to, and not in lieu of, their rights to registration under Sections 2.1 and 2.3.

2.3 Registration on Form S-3.

(a) Subject to Section 2.1(b) and Section 2.8, if at any time or from time to time after the Company has become eligible to register securities on Form S-3 (or any successor form), and while the Company is so eligible, Holders request in writing (specifying that such request is being made pursuant to this Section 2.3) that the Company file under the Act a registration statement on Form S-3 (or any successor form) for a public offering from which the total gross proceeds reasonably expected to be received by the requesting Holders is at least \$1,000,000, then the Company shall use its best efforts to cause such shares to be registered on Form S-3 (or any successor form).

(b) The Holders' rights to registration under this Section 2.3 are in addition to, and not in lieu of, their rights to registration under Sections 2.1 and 2.2.

2.4 Obligations of the Company. Whenever required under this Agreement to use its best efforts to effect the registration of any Registrable Securities, the Company shall, as expeditiously as reasonably possible:

(a) Prepare and file with the Commission a registration statement covering such Registrable Securities and use its best efforts to cause such registration statement to be declared effective by the Commission as expeditiously as possible and to keep such registration effective until the earlier of (i) the date when all Registrable Securities covered by the registration statement have been sold or (ii) 150 days from the effective date of the registration statement; provided, that before filing a registration statement or prospectus or any amendments or supplements thereto, the Company will furnish to each Holder of Registrable Securities covered by such registration statement and the underwriters, if any, copies of all such documents proposed to be filed (excluding exhibits, unless any such person shall specifically request exhibits), which documents will be subject to the review of such Holders and underwriters, and the Company will not file such registration statement or any amendment thereto or any prospectus or any supplement thereto (including any documents incorporated by reference therein) with the Commission if (i) the Holders of a majority of the Registrable Securities covered by such registration statement or the underwriters, if any, reasonably object to such filing or (ii) information in such registration statement or prospectus concerning a particular selling Holder has changed and such Holder or the underwriters, if any, reasonably objects;

(b) Prepare and file with the Commission such amendments and post-effective amendments to such registration statement as may be necessary to keep such registration statement effective during the period referred to in Section 2.4(a) and to comply with the provisions of the Act with respect to the disposition of all securities covered by such registration statement; and cause the prospectus to be supplemented by any required prospectus supplement and to file such supplement with the Commission pursuant to Rule 424 under the Act;

(c) Furnish to the selling Holders such numbers of copies of such registration statement, each amendment thereto, the prospectus included in such registration statement (including each preliminary prospectus), each supplement thereto and such other documents as they may reasonably request in order to facilitate the disposition of Registrable Securities owned by them;

(d) Use its best efforts to register and qualify the Registrable Securities under such other securities laws of such jurisdictions as shall be reasonably requested by any selling Holder and do any and all other acts and things which may be reasonably necessary or advisable to enable such selling Holder to consummate the disposition of the Registrable Securities owned by such Holder in such jurisdictions; provided, that the Company shall not be required in connection therewith or as a condition thereto to qualify to transact business or to file a general consent to service of process in any such states or jurisdictions and that, notwithstanding any provision of this Agreement to the contrary, to the extent that any jurisdiction in which the Registrable Securities are to be qualified requires that expenses incurred in connection with the qualification of the Registrable Securities in that jurisdiction be borne by selling shareholders, then such expenses shall be payable by the selling Holders pro rata;

(e) Promptly notify each selling Holder of such Registrable Securities at any time when a prospectus relating thereto is required to be delivered under the Act of the happening of any event which results in the prospectus included in such registration statement containing an untrue statement of a material fact or omitting a fact necessary to make the statements therein not misleading; and, at the request of any such Holder, the Company will prepare a supplement or amendment to such prospectus so that, as thereafter delivered to the purchasers of such Registrable Securities, such prospectus will not contain an untrue statement of a material fact or omit to state any fact necessary to make the statements therein not misleading;

(f) Provide a transfer agent and registrar for all such Registrable Securities not later than the effective date of such registration statement;

(g) Enter into such customary agreements (including underwriting agreements in customary form for a primary offering) and take all such other actions as the Holders of a majority of the Registrable Securities being sold or the underwriters, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities (including, without limitation, effecting a stock split or a combination of shares);

(h) Make available for inspection by any selling Holder of Registrable Securities, any underwriter participating in any disposition pursuant to such registration statement and any attorney, accountant or other agent retained by any such selling Holder or underwriter, all financial and other records, pertinent corporate documents and properties of the Company, and cause the officers, directors, employees and independent accountants of the Company to supply all information reasonably requested by any such seller, underwriter, attorney, accountant or agent in connection with such registration statement;

(i) Promptly notify the Holders of Registrable Securities and the underwriters, if any, of the following events and (if requested by any such person) confirm such notification in writing: (1) the filing of the prospectus or any prospectus supplement and the registration statement and any amendment or post-effective amendment thereto and, with respect to the registration statement or any post-effective amendment thereto, the declaration of the effectiveness of such documents; (2) any requests by the Commission for amendments or supplements to the registration statement or the prospectus or for additional information; (3) the issuance or threat of issuance by the Commission of any stop order suspending the effectiveness of the registration statement or the initiation of any proceedings for that purpose; and (4) the receipt by the Company of any notification with respect to the suspension of the qualification of the Registrable Securities for sale in any jurisdiction or the initiation or threat of initiation of any proceeding for such purpose;

(j) Use its best efforts to prevent the entry of any order suspending the effectiveness of the registration statement and to obtain the withdrawal of any such order, if entered, as expeditiously as possible;

(k) If reasonably requested by any underwriter or a selling Holder of Registrable Securities in connection with any underwritten offering, promptly incorporate in a prospectus supplement or post-effective amendment such information as the underwriters and the Holders of a majority of the Registrable Securities covered by such registration statement reasonably request be included therein relating to the sale of the Registrable Securities, including, without limitation, information with respect to the number of Registrable Securities being sold to such underwriters, the purchase price being paid therefor by such underwriters and any other terms of the underwritten offering of the Registrable Securities to be sold pursuant thereto, and make all required filings of such prospectus supplement or post-effective amendment promptly after being notified of the matters to be incorporated in such prospectus supplement or post-effective amendment;

(l) Prior to the filing of any document which is to be incorporated by reference into the registration statement or the prospectus (after the initial filing of the registration statement with the Commission), (i) promptly provide copies of such document to counsel for the selling Holders of the Registrable Securities and the counsel for the underwriters, if any; (ii) make representatives of the Company available for discussion of such document; and (iii) make such changes in such document prior to the filing thereof as counsel for such Holders or underwriters may reasonably request;

(m) Cooperate with the selling Holders of Registrable Securities and the underwriters, if any, to facilitate the timely preparation and delivery of certificates representing Registrable Securities to be sold that do not bear restrictive legends, and enable such Registrable Securities to be in such lots and registered in such names as the underwriters may request at least two business days prior to any delivery of Registrable Securities to the underwriters;

(n) Provide a CUSIP number for all Registrable Securities not later than the effective date of the registration statement; and

(o) Use its best efforts to obtain an opinion from the Company's counsel and a "cold comfort" letter from the Company's independent public accountants in customary form and covering such matters as are customarily covered by such opinions and "cold comfort" letters delivered to underwriters in underwritten public offerings, which opinion and letter shall be reasonably satisfactory to the underwriter, and to the Holders of a majority of the Registrable Securities participating in such offering, and furnish to each Holder participating in the offering and to each underwriter a copy of such opinion and letter addressed to such Holder or underwriter.

2.5 Furnish Information. It shall be a condition precedent to the obligations of the Company (i) to take any action pursuant to this Agreement that the Holders shall furnish to the Company such information regarding them, the Registrable Securities held by them and the intended method of disposition of such Registrable Securities as the Company shall reasonably request and as shall be required in connection with the action to be taken by the Company; and (ii) to cause any registration pursuant to this Agreement to have become effective for the Holders to have exercised their rights of conversion or exercise, as the case may be, with respect to any Registrable Securities proposed to be registered.

2.6 Suspension of Disposition of Registrable Securities. Each selling Holder of Registrable Securities agrees that, upon receipt of any notice from the Company of the happening of any event of the kind described in Section 2.4(e), such Holder will forthwith discontinue disposition of Registrable Securities until such Holder receives a supplemented or amended prospectus as contemplated by Section 2.4(e) or is advised in writing by the Company (the "Advice") that the use of the prospectus may be resumed, and until such Holder has received copies of any additional or supplemental filings that are incorporated by reference in the prospectus, and, if so directed by the Company, such Holder will deliver to the Company (at the expense of the Company) all copies, other than permanent file copies then in such Holder's possession, of the prospectus covering such Registrable Securities current at the time of receipt of such notice. In the event the Company shall give any such notice, the time periods set forth in Section 2.4(a) shall be extended by the number of days during the period from and including the date of the giving of such notice pursuant to Section 2.4(e) to and including the date when each selling Holder of Registrable Securities shall have received the copies of the supplemented or amended prospectus contemplated by Section 2.4(e) or the Advice.

2.7 Expenses of Registration. All expenses incurred in connection with a registration pursuant to Sections 2.1, 2.2 and 2.3 (excluding underwriters' discounts and commissions, but including the reasonable fees and expenses of one legal counsel to the Holders, not to exceed \$20,000 per registration), including, without limitation all registration and

qualification fees, printing and accounting fees, fees and disbursements of counsel for the Company shall be borne by the Company; provided, however, that (i) the Company shall not be required to pay for any expenses of any registration proceeding begun pursuant to Section 2.1 if the registration request is subsequently withdrawn at the request of the Holders, unless (A) the Holders agree to forfeit their right to one demand registration pursuant to Section 2.1 or (B) there has been a withdrawal or postponement of such registration by the Company due to a Valid Business Reason, and (ii) if there has been a material adverse change in the business or prospects of the Company after the date of any demand for registration made pursuant to Section 2.1, which change has caused such request to be withdrawn, then the Holders shall not be required to pay any of the expenses for such registration and shall retain all of their rights under Section 2.1.

2.8 Underwriting Requirements; Priorities.

(a) The Holders of a majority of the Registrable Securities included in any registration under Sections 2.1 or 2.3 will have the right to select the underwriter(s) and manager(s) to administer the offering, if any, subject to the approval of the Company, which will not be unreasonably withheld. The Company will not include in any registration under Sections 2.1 or 2.3 any securities that are not Registrable Securities without the written consent of the Holders of a majority of the Registrable Securities requesting such registration. If the managing underwriters in an underwritten public offering advise the Company in writing that, in their opinion, the number of Registrable Securities and other securities requested to be included exceeds the number of Registrable Securities and other securities that can be sold in an orderly manner and at the desired price in such offering, the Company will include in such registration (i) first, prior to the inclusion of any securities that are not Registrable Securities, the number of Registrable Securities requested to be included that, in the opinion of such managing underwriters, can be sold, pro rata among the respective Holders on the basis of the amount of Registrable Securities requested to be included in such registration, (ii) second, all securities proposed to be included by the Company, and (iii) third, all other securities permitted to be included in such registration.

(b) The Company will have the right to select the underwriter(s) and manager(s) to administer any offering to which Section 2.2 is applicable. If in any registration under Section 2.2 the managing underwriters advise the Company in writing that, in their opinion, the number of securities requested to be included in such registration exceeds the number which can be sold in an orderly manner and at the desired price in such offering, the Company will include in such registration (i) first, all securities proposed to be included by the Company, (ii) second, the Registrable Securities requested to be included in such registration by the Holders, pro rata among the Holders thereof on the basis of the number of Registrable Securities requested to be included in such registration, and (iii) third, all other securities permitted to be included in such registration.

(c) No person may participate in any underwritten registration hereunder unless such person (i) agrees to sell such person's securities on the basis provided in any underwriting arrangements containing reasonable and customary terms for transactions of that type or as otherwise approved by the Holders of a majority of the Registrable Securities being included in such underwritten registration; and (ii) completes and

executes all questionnaires, powers of attorney, customary indemnities, underwriting agreements and other documents required under the term of such underwriting arrangements.

2.9 Termination of the Company's Obligations under Section 2.1. The Company shall have no further obligations pursuant to Section 2.1 with respect to any request or requests made by any Holder after the Company has effected one (1) registration under Section 2.1(a)(i) and one (1) registration under Section 2.1(a)(ii) with respect to which the Company has complied with its obligations hereunder or under which all Registrable Securities covered thereby have been sold pursuant thereto.

2.10 Reports under the 1934 Act. With a view to making available to the Holders the benefits of Rule 144 promulgated under the Act and any other rule or regulation of the Commission that may at any time permit a Holder to sell securities of the Company to the public without registration, the Company agrees to use its best efforts to:

(a) make and keep public information available, as those terms are understood and defined in Rule 144, at all times subsequent to ninety (90) days after the effective date of the first registration statement covering an underwritten public offering filed under the Act by the Company;

(b) file with the Commission in a timely manner all reports and other documents required of the Company under the Act and the 1934 Act at any time after it is subject to such registration requirements; and

(c) furnish to any Holder, so long as such Holder owns any of the Registrable Securities, forthwith upon request a written statement by the Company that it has complied with the reporting requirements of Rule 144 (at any time after ninety (90) days after the effective date of said first registration statement filed by the Company), the Act and the 1934 Act (at any time after it has become subject to such reporting requirements), a copy of the most recent annual or quarterly report of the Company, and such other reports and documents so filed by the Company as may be reasonably requested by any Holder in availing any Holder of any rule or regulation of the Commission permitting the selling of any such securities without registration.

2.11 Certain Limitations in Connection with Future Grants of Registration Rights. From and after the Effective Date, the Company shall not enter into any agreement with any holder or prospective holder of any securities of the Company providing for the granting to such holder of registration rights unless such agreement includes a provision that, in the case of a registration involving an underwritten offering under Section 2.1, protects the Holders in the manner contemplated by Section 2.8 if marketing factors require a limitation on the number of securities to be included in the underwritten offering.

2.12 Transfer of Registration Rights. The registration rights granted hereunder may be transferred in whole or in part in connection with the transfer of Registrable Securities at any time as long as the Company receives prior written notice from the Holder at the time of such transfer stating the name and address of the transferee and identifying the Registrable Securities with respect to which the rights hereunder are being assigned.

2.13 Indemnification. In the event any Registrable Securities are included in a registration statement under this Agreement:

(a) To the full extent permitted by law, the Company will, and hereby does indemnify and hold harmless each Holder requesting or joining in a registration, each director, officer, partner, employee, or agent for such Holder, any underwriter (as defined in the Act) for such Holder, and each person, if any, who controls such Holder or underwriter within the meaning of Section 15 of the Act, against any losses, claims, damages or liabilities, joint or several, to which they may become subject under the Act and applicable state securities laws insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based on any untrue or alleged untrue statement of any material fact contained in such registration statement, including any preliminary prospectus or final prospectus contained therein or any amendments or supplements thereto, or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading or arise out of any violation by the Company of the Act, any rule or regulation promulgated under the Act or state securities laws applicable to the Company and relating to action or inaction required of the Company in connection with any such registration; and will reimburse each such person or entity for any legal or other expenses reasonably incurred by them in connection with investigating or defending any such loss, claim, damage, liability, or action; provided, however, that the indemnity agreement contained in this Section 2.13(a) shall not apply to amounts paid in settlement of any such loss, claim, damage, liability, or action if such settlement is effected without the consent of the Company (which consent shall not be unreasonably withheld) nor shall the Company be liable in any such case for any such loss, claim, damage, liability or action to the extent that it arises out of or is based upon an untrue statement or alleged untrue statement or omission or alleged omission made in connection with such registration statement, preliminary prospectus, final prospectus, or amendment or supplement thereto, in reliance upon and in conformity with written information furnished expressly for use in connection with such registration by or on behalf of any such Holder, underwriter or controlling person.

(b) To the full extent permitted by law, each Holder requesting or joining in a registration under this Agreement will indemnify and hold harmless the Company, each of its directors and officers, each person who controls the Company within the meaning of the Act, and any underwriter (within the meaning of the Act) for the Company, each other selling Holder and each person, if any, who controls such other selling Holder within the meaning of Section 15 of the Act against any losses, claims, damages or liabilities, joint or several, to which the Company or any such director, officer, controlling person or underwriter may become subject, under the Act and applicable state securities laws, insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based upon any untrue statement or alleged untrue statement of any material fact contained in such registration statement, including any preliminary prospectus or final prospectus contained therein or any amendment or supplement thereto, or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading in light of the circumstances under which they were

made, in each case to the extent, but only to the extent, that such untrue statement or alleged untrue statement or omission or alleged omission was made in such registration statement, preliminary or final prospectus, or amendments or supplements thereto, in reliance upon and in conformity with written information furnished by such Holder expressly for use in connection with such registration; and each such Holder will reimburse any legal or other expenses reasonably incurred by the Company or any such director, officer, controlling person or underwriter in connection with investigating or defending any such loss, claim, damage, liability or action; provided, however, that the indemnity agreement contained in this Section 2.13(b) shall not apply to amounts paid in settlement of any such loss, claim, damage, liability or action if such settlement is effected without the consent of such Holder (which consent shall not be unreasonably withheld). Notwithstanding the foregoing, in no event shall the liability of any selling Holder of Registrable Securities hereunder be greater than the dollar amount of the proceeds received by such Holder upon the sale of the Registrable Securities giving rise to such indemnification obligation.

(c) Promptly after receipt by an indemnified party under this Section 2.13 of notice of the commencement of any action or knowledge of a claim that would, if asserted, give rise to a claim for indemnity hereunder, such indemnified party will, if a claim in respect thereof is to be made against any indemnifying party under this Section 2.13, notify the indemnifying party in writing of the commencement thereof or knowledge thereof and the indemnifying party shall have the right to participate in, and, to the extent the indemnifying party so desires, jointly with any other indemnifying party similarly notified, to assume the defense thereof with counsel mutually satisfactory to the parties. The failure to notify an indemnifying party promptly of the commencement of any such action or of the knowledge of any such claim, if prejudicial to its ability to defend such action, shall relieve such indemnifying party of any liability to the indemnified party under this Section 2.13, but the omission so to notify the indemnifying party will not relieve him of any liability that he may have to any indemnified party otherwise than under this Section.

2.14 Contribution by Indemnifying Party.

(a) If the indemnification provided for in Section 2.13 is unavailable to an indemnified party hereunder in respect of any losses, claims, damages, liabilities or expenses referred to therein, then each indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages, liabilities or expenses in such proportion as is appropriate to reflect the relative fault of the indemnifying party and indemnified parties in connection with the actions which resulted in such losses, claims, damages, liabilities or expenses, as well as any other relevant equitable considerations. The relative fault of each indemnifying party and indemnified parties shall be determined by reference to, among other things, whether any action in question, including any untrue or alleged untrue statement of a material fact or omission or alleged omission to state a material fact, has been made by, or relates to information supplied by, such indemnifying party or parties or indemnified parties, and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such action. The amount paid or payable by a party as a result of the losses, claims, damages, liabilities and expenses

referred to above shall be deemed to include any reasonable legal or other fees or expenses incurred by such party in connection with any investigation or proceeding.

(b) The parties hereto agree that it would not be just and equitable if contribution pursuant to this Section 2.14 were determined by pro rata allocation or by any other method of allocation which does not take account of the equitable considerations referred to in Section 2.14(a). No Person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any Person who was not guilty of such fraudulent misrepresentation.

3. Amendments and Waivers. Except as provided below or as otherwise provided herein, the provisions of this Agreement may not be amended, waived, modified or supplemented without the prior written consent of the Company and the holders of (i) a majority of the outstanding Series A Registrable Securities and Series B Registrable Securities and (ii) at least 65% of the outstanding Series C Registrable Securities; provided, however, that if any amendment, waiver, modification or supplement (but not any termination) would (a) treat the Series A Investors different from the manner in which it would treat the Series B Investors, then such amendment, waiver, modification or supplement shall not be effective against the Series A Investor without the written consent of the holders of a majority of the outstanding Series A Registrable Securities and shall not be effective against the Series B Investors without the written consent of the holders of a majority of the outstanding Series B Registrable Securities, or (b) treat any Series A Investor, Series B Investor or Series C Investor, as the case may be, in a manner different from the manner in which it would treat all other Series A Investors, Series B Investors or Series C Investors, as the case may be, such amendment, waiver, modification or supplement shall not be effective against the differently treated Investor without the written consent of such Investor. Any amendment, waiver, modification or supplement effected in accordance with this Section 3 shall be binding upon the Company and, except as provided in the immediately preceding sentence, each Investor, whether or not such Investor executed such amendment, waiver, modification or supplement.

4. Notices. All notices and other communications required or permitted hereunder shall be in writing and shall be mailed by certified mail, postage prepaid, or otherwise delivered by hand or by nationally-recognized overnight delivery service to the address set forth beneath each party's counterpart signature hereto; provided that, notwithstanding the foregoing, notices delivered in any other manner (including, without limitation, by email) shall be effective with respect to any particular Investor if and when actually received by that Investor. All such notices and communications required hereunder shall be deemed to have been received; at the time delivered by hand, if personally delivered; three business days after being deposited in the mail, postage prepaid, if mailed; and on the second business day after deposit with a nationally-recognized overnight courier.

5. Counterparts. This Agreement may be executed in any number of counterparts and by the parties hereto in separate counterparts, each of which when so executed shall be deemed to be an original and all of which taken together shall constitute one and the same agreement.

6. Headings. The headings in this Agreement are for convenience of reference only and shall not limit or otherwise affect the meaning hereof.

7. Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of Delaware, without regard to the principles of conflicts of laws.

8. Severability. In the event that any one or more of the provisions contained herein, or the application thereof in any circumstance, is held invalid, illegal or unenforceable, the validity, legality and enforceability of any such provision in every other respect and of the remaining provisions contained herein shall not be affected or impaired thereby.

9. Effectiveness; Entire Agreement. Unless and until the Effective Date occurs, this Agreement shall not become effective or affect the Current Agreement, and the Current Agreement shall continue in full force and effect. Upon the occurrence of the Effective Date, this Agreement will automatically amend, restate and supersede the Current Agreement in its entirety. Notwithstanding anything to the contrary contained in this Agreement, if the Effective Date does not occur on or before December 31, 2004, this Agreement shall not become effective and be of no force or effect. As of the Effective Date, this Agreement is intended by the parties as a final expression of their agreement and to be a complete and exclusive statement of the agreement and understanding of the parties hereto in respect of the subject matter contained herein; provided that any waiver of convertible preferred stock conversion price adjustment previously made by a Series A Investor or Series B Investor pursuant to Section 4.7 of the Original Agreement shall survive such amendment and restatement and continue in full force and effect. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to in the Current Agreement and herein, with respect to the registration rights granted by the Company.

10. Parties Benefited. Nothing in this Agreement, express or implied, is intended to confer upon any third party any rights, remedies, obligations or liabilities.

IN WITNESS WHEREOF, the parties have executed this Third Amended and Restated Investor Rights Agreement as of the date first above written.

TARGACEPT, INC.
200 East First Street, Suite 300
Winston-Salem, North Carolina 27101-4165

By: _____ /s/ J. DONALD DEBETHIZY
Name: J. Donald deBethizy
Title: President and CEO

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

NOMURA INTERNATIONAL PLC Nomura House
1 St. Martin's-le-Grand
London EC1A 4NP
England

By: _____ /s/ DENISE POLLARD-KNIGHT
Name: Denise Pollard-Knight
Title: Head of Phase 4 Venture

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

NEW ENTERPRISE ASSOCIATES 10, LIMITED
PARTNERSHIP
1119 St. Paul Street
Baltimore, Maryland 21202

By: NEA Partners 10, Limited Partnership,
General Partner

By: _____ /s/ EUGENE A. TRAINOR, III
Name: Eugene A. Trainor, III
Title: Administrative General Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

NEA VENTURES, 2002 LIMITED PARTNERSHIP
1119 St. Paul Street
Baltimore, Maryland 21202

By: _____ /s/ PAMELA J. CLARK
Name: Pamela J. Clark
Title: General Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

CDIB BIOSCIENCE VENTURES I, INC.
30th Floor, 99 Tun Hwa South Road
Section 2, Taipei 106
Taiwan

By: _____ /s/ BENNY T. HU
Name: Benny T. Hu
Title: Chairman

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

EASTON HUNT CAPITAL PARTNERS, L.P.
641 Lexington Avenue, 21st Floor
New York, New York 10022

By: EHC GP, LP, its General Partner,

By: EHC Inc., its General Partner

By: _____ /s/ JOHN H. FRIEDMAN
Name: John H. Friedman
Title: President

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

R.J. REYNOLDS TOBACCO HOLDINGS, INC.
401 North Main St.
Winston-Salem, NC 27102

By: _____ /s/ CHARLES A. BLIXT
Name: Charles A. Blixt
Title: EVP & General Counsel

Acknowledged and agreed to:

R.J. REYNOLDS TOBACCO COMPANY

By: _____ /s/ CHARLES A. BLIXT
Name: Charles A. Blixt
Title: EVP & General Counsel

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

EUCLIDSR PARTNERS, L.P.
Four Tower Bridge
200 Barr Harbor Drive, Suite 250
West Conshohocken, PA 19428-2977

By: EUCLIDSR ASSOCIATES, L.P. its general
partner

By: _____ /s/ ELAINE V. JONES
Name: Elaine V. Jones
Title: General Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

EUCLIDSR BIOTECHNOLOGY
PARTNERS, L.P.
Four Tower Bridge
200 Barr Harbor Drive, Suite 250
West Conshohocken, PA 19428-2977

By: EUCLIDSR BIOTECHNOLOGY
ASSOCIATES, L.P., its general partner

By: _____ /s/ ELAINE V. JONES
Name: Elaine V. Jones
Title: General Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

BURRILL BIOTECHNOLOGY CAPITAL FUND, L.P.
One Embarcadero Center, Suite 2700
San Francisco, California 94111

By: Burrill & Company (Biotechnology GP, LLC,
its General Partner

By: _____ /s/ G.S. BURRILL
Name: G.S. Burrill
Title:

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

FCPR CDC Innovation 2000, a venture capital fund represented by CDC IXIS Innovation, its management company ("Societe de gestion") with a share capital of EUR 762,000

Tour Maine Montparnasse
33 Avenue du Maine – B.P. 180
75755 Paris Cedex

By: _____ 05/13/04 /s/ MR. STEPHANE BOUDON

Name: Mr. Stephane Boudon
Title: CEO

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

Academy Venture Fund, LLC
920 Main Campus Drive, Suite 400
Raleigh, North Carolina 27606
By: Academy Ventures, LLC, Manager

By: _____ /s/ JOHN CIANNAMEA
Name: John Ciannamea
Title: Manager

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

Auriga Ventures, a venture capital fund represented by Auriga Partners, a French limited company with a share capital of Eur 456,250, having its registered office at 18 Avenue Matignon, 75008 PARIS (France) registered with the Paris Trade and Companies registry under number B 419 156 351

By: _____ /s/ BERNARD DAUGERAS
Name: Bernard Daugeras
Title: Managing Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

GENAVENT FUND
c/o Société Générale Asset Management
2, place de la Coupole,
92078 Paris – La Défense cedex
France Attn: Jean Grimaldi

By: Société Générale Asset Management,
S.A., its Manager

By: _____ /s/ JEAN V. GRIMALDI
Name: Jean V. Grimaldi
Title: Head of Private Equity

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

FCPR SGAM BIOTECHNOLOGY FUND
Represented by SG Asset Management, its management company with a share capital of 292 800 000 euros, having its registered office at 2, place de la Coupole, 92078 Paris – La Défense cedex France, registered with the Nanterre Trade and Companies registry under the number B 308 396308

By: _____ /s/ JEAN V. GRIMALDI
Name: Jean V. Grimaldi
Title: Head of Private Equity

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

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FCPR SGAM BIOTECHNOLOGY FUND
Represented by SG Asset Management, its management
company with a share capital of 292 800 000 euros, having its
registered office at 2, place de la Coupole, 92078 Paris – La
Défense cedex France, registered with the Nanterre Trade and
Companies registry under the number B 308 396308

By: _____ /s/ GREG BETTERTON
Name: Greg Betterton
Title: Manager

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

JAFCO G-9(B) Venture Capital Investment
Limited Partnership
Tekko Building, 1-8-2, Marunouchi, Chiyoda-Ku
Tokyo 100-005, Japan
By: JAFCO Co., Ltd.
Its General Partner

By: _____ /s/ H. AGATA
Name: Hisaji Agata
Title: Managing Director

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

Cogene Biotech Ventures
Five Post Oak Park
4400 Post Oak Parkway, Suite 1400
Houston, Texas 77027

By: _____ /s/ C. THOMAS CASKEY
Name: C. Thomas Caskey
Title: President/CEO

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

Rock Castle Ventures, L.P.
23822 W. Valencia Blvd., Ste 202
Valencia, CA 91355
By: Rock Castle Management LLC,
its General Partner

By: _____ /s/ ERIC Y. SATO
Name: Eric Y. Sato
Title: General Partner

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

Oxford Bioscience Partners IV L.P.
By: OBP Management IV L.P., General Partner

By: _____ /s/ ALAN G. WALTON

Name:
Title:

COUNTERPART SIGNATURE PAGE

TARGACEPT, INC.
THIRD AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT

IN WITNESS WHEREOF, the undersigned has executed this Third Amended and Restated Investor Rights Agreement under seal as of this 12th day of May 2004.

mRNA Fund II L.P.

By: OBP Management IV L.P., General Partner

By: _____ /s/ ALAN G. WALTON

Name:
Title:

**Amendment No. 1 to
Third Amended and Restated Investor Rights Agreement**

THIS AMENDMENT NO. 1 to the Third Amended and Restated Investor Rights Agreement dated December 6, 2004 (this "**Amendment**") amends the Third Amended and Restated Investor Rights Agreement dated May 12, 2004 (the "**Future IRA**") by and among Targacept, Inc. (the "**Company**") and the holders of shares of the Company's Series C Convertible Preferred Stock, \$0.001 par value per share ("**Series C Stock**"), Series B Convertible Preferred Stock, \$0.001 par value per share ("**Series B Stock**"), or Series A Convertible Preferred Stock, \$0.001 par value per share ("**Series A Stock**" and, together with the Series C Stock and Series B Stock, "**Preferred Stock**") party thereto. Capitalized terms used herein and not otherwise defined shall have the meanings ascribed to them in the Future IRA.

R E C I T A L S:

WHEREAS, the Future IRA was entered into in contemplation of an initial public offering of the Company's common stock in order to amend, effective as of the closing of such initial public offering, the Company's Second Amended and Restated Investor Rights Agreement dated November 26, 2002, as amended (the "**Current IRA**"), which is currently in effect; and

WHEREAS, by its terms, the Future IRA will not become effective or affect the Current IRA unless and until the prospective initial public offering is completed and will not become effective at all if such initial public offering is not completed on or before December 31, 2004 (the "**Trigger Date**"); and

WHEREAS, Section 3 of the Future IRA provides that the Future IRA may be amended only with the prior written consent of the Company and the holders of a majority of the outstanding Series A Registrable Securities and Series B Registrable Securities and at least 65% of the outstanding Series C Registrable Securities (collectively, the "**Required Investors**"); and

WHEREAS, the prospective initial public offering may not be completed on or before the Trigger Date, and the Company and the undersigned holders of Preferred Stock, constituting the Required Investors, desire to amend the Future IRA as provided herein to extend the Trigger Date;

NOW, THEREFORE, the undersigned parties agree as follows:

1. Section 2.1(a) of the Future IRA is hereby amended by deleting the first sentence in its entirety and replacing it with the following:

"Subject to the other provisions of this Section 2.1, Section 2.8 and Section 2.9, if, at any time or from time to time following the Eligibility Date (but in no event prior to (x) six months after the effective date of the first registration of the Company's securities on Form S-1 or (y) three months after the effective date of any other registration of the Company's securities, other than registrations on Form S-4, Form S-8 or comparable or successor forms and other than registrations for the account of selling stockholders on Form S-3 or a comparable or successor form), the Company shall receive a written

request (specifying that it is being made pursuant to this Section 2.1) from (i) Holders of at least a majority of the Series A Registrable Securities and Series B Registrable Securities, considered together, or (ii) Holders of Series C Registrable Securities that the Company file a registration statement under the Act covering the registration for offer and sale of (A) in the case of clause (i) above, at least thirty percent (30%) of all Series A Registrable Securities and Series B Registrable Securities, considered together, or (B) in the case of clause (ii) above, at least (1) thirty percent (30%) of all Series C Registrable Securities or (2) a number of Series C Registrable Securities for which the total gross proceeds in a public offering reasonably expected to be received by the requesting Holders is at least \$7,500,000, then the Company shall, within ten (10) business days notify in writing all other Holders of such request.”

2. Section 9 of the Future IRA is hereby amended by replacing “December 31, 2004” therein with “June 30, 2005.”

3. As expressly amended hereby, the Future IRA shall continue in full force and effect.

4. For the avoidance of doubt, as used in the Future IRA and the Current IRA, the term “Series C Stock” shall include, without limitation, shares of Series C Stock issued and sold pursuant to the Series C Convertible Preferred Stock Purchase Agreement entered into on or about the date hereof.

[signature page follows]

TARGACEPT, INC.

By: /s/ J. Donald deBethizy
Name: J. Donald deBethizy
Title: President & CEO

R.J. REYNOLDS TOBACCO HOLDINGS, INC.

By: /s/ Charles A. Blixt
Name: Charles A. Blixt
Title: President

EUCLIDSR PARTNERS, L.P.

By: EuclidSr Associates, L.P.,
its general partner

By: /s/ Elaine V. Jones
Elaine V. Jones
General Partner

EUCLIDSR BIOTECHNOLOGY PARTNERS, L.P.

By: EuclidSr Biotechnology Associates, L.P.,
its general partner

By: /s/ Elaine V. Jones
Elaine V. Jones
General Partner

BURRILL BIOTECHNOLOGY CAPITAL FUND, L.P.

By: Burrill & Company (Biotechnology GP), LLC,
its General Manager

By: /s/ G. S. Burrill
G. Steven Burrill
Managing Member

[signatures continue on following page]

GENAVENT FUND

By: Société Générale Asset Management, S.A.,
its Manager

By: /s/ Ferriere

Corinne Ferriere
Deputy Head of Private Equity

FCPR SGAM AI BIOTECHNOLOGY FUND
Represented by SGAM Alternative Investments, its
management company with a share capital of 35 576
725 euros, having its registered office at 2, place de la Coupole,
92078 Paris – La Défense cedex France,
registered with the Nanterre Trade and Companies
registry under the number B 410 704 571

By: /s/ Ferriere

Corinne Ferriere
Deputy Head of Private Equity

FCPR CDC INNOVATION 2000, a venture
capital fund represented by CDC ENTREPRISES
INNOVATION, its management company
("Societe de gestion") with a share capital of
EUR 762,000

By: /s/ T. Laugel

Name: T. Laugel
Title: Director d'investissement

ADVENT PRIVATE EQUITY FUND II,
'A' LIMITED PARTNERSHIP
ADVENT PRIVATE EQUITY FUND II,
'B' LIMITED PARTNERSHIP
ADVENT PRIVATE EQUITY FUND II,
'C' LIMITED PARTNERSHIP
ADVENT PRIVATE EQUITY FUND II,
'D' LIMITED PARTNERSHIP

By: Advent Venture Partner, General Partner

By: /s/ Patrick Lee

Name: Patrick Lee
Title: General Partner

[signatures continue on following page]

NOMURA PHASE4 VENTURES LIMITED AS MANAGER
ON BEHALF OF INTERNATIONAL PLC AND NOMURA
PHASE4 VENTURES LP

By: /s/ Denise Pollard-Knight
Name: Denise Pollard-Knight
Title: Head of Nomura Phase4 Ventures Ltd.

NEW ENTERPRISE ASSOCIATES 10, LIMITED
PARTNERSHIP

By: NEA Partners 10, Limited Partnership, General Partner

By: /s/ E. A. Trainor
Name: Eugene A. Trainor, III
Administrative General Partner & Chief Operating Officer

NEA VENTURES, 2002 LIMITED PARTNERSHIP

By: /s/ Pamela J. Clark
Pamela J. Clark
General Partner

CDIB BIOSCIENCE VENTURES I, INC.

By: /s/ Benny T. Hu
Name: Benny T. Hu
Title: Chairman

JAFCO G-9(A) VENTURE CAPITAL INVESTMENT
LIMITED PARTNERSHIP

By: JAFCO CO., LTD., its general partner

By: /s/ Tomio Kezuka
Name: Tomio Kezuka
Title: Executive Vice President

[signatures continue on following page]

By: /s/ Tomio Kezuka

Name: Tomio Kezuka

Title: Executive Vice President

NORTH CAROLINA

FIRST LEASE AMENDMENT

FORSYTH COUNTY

This First Lease Amendment ("Amendment"), made effective as of the 1st day of January, 2005 (the "Amendment Date"), by and between Wake Forest University Health Sciences, a North Carolina non-profit corporation having its principal office in Winston-Salem, North Carolina, ("Landlord"); and Targacept, Inc., a Delaware corporation, having its principal office in Winston-Salem, North Carolina ("Tenant") amends that Lease entered into between the parties effective August 1, 2002 (the "Lease").

WITNESSETH:

WHEREAS, Landlord and Tenant desire to amend the Lease upon the terms and conditions and for the rents reserved as further set forth herein,

NOW, THEREFORE, Landlord and Tenant hereby agree as follows:

1. Unless otherwise agreed herein, all of the capitalized terms of this Amendment shall have the same meanings ascribed to them in the Lease.
2. That the Lease is amended in the following respects:
 - A. By deleting Exhibit A of the Lease and substituting in lieu thereof the attached Exhibit A, which adds an additional 1000 rentable square feet of space from the first floor of the Building to the Demised Premises.
 - B. By deleting paragraph 1.2 of the Lease and renumbering paragraph 1.3 as paragraph 1.2.
 - C. By deleting paragraph 2.3 of the Lease and substituting in lieu thereof the following:

"2.3 Landlord hereby grants Tenant the following options to lease additional space in the building (each, an "Option to Lease"):

2.3.1 First Floor Option

Landlord hereby grants to Tenant the option to lease up to 12,338 additional rentable square feet of space on the first floor of the building (the "First Floor Option Space"), provided Tenant shall have paid to Landlord on or before January 1, 2005 (the "Amendment Date") the sum of \$37,014 (\$3.00 per rsf) as a "space hold fee" to secure this right for the period from the Amendment

Date through March 31, 2006 (the "First Floor Option Period"). Tenant will exercise this Option to Lease, if it elects exercise, by giving written notice to Landlord not later than 60 days prior to Tenant's intended occupancy date for such First Floor Option Space (the "First Floor Occupancy Effective Date"). Exercise of this Option to Lease shall effect a lease of the First Floor Option Space from the First Floor Occupancy Effective Date through the balance of the Initial Term and, only if Targacept elects both to exercise the Renewal Option and to continue to lease the First Floor Option Space during the Renewal Term, for the Renewal Term. If the Option to Lease the First Floor Option Space is exercised, (a) the First Floor Option Space shall thereupon become part of the Demised Premises for the Initial Term and, subject to the conditions set forth in the preceding sentence, the Renewal Term and (b) Tenant will pay Rent for such First Floor Option Space during the Initial Term and, subject to the conditions set forth in the preceding sentence, the Renewal Term as set forth in paragraphs 3.1 and 3.2; provided that (i) an amount equal to (A) \$2,467.60 (the space hold fee divided by the 15 months in the First Floor Option Period) times (B) the number of calendar months for which the first day occurs after the date on which Targacept exercises the Option to Lease the First Floor Option Space and before March 31, 2006 shall be applied as a credit against the first Rent due for the First Floor Option Space and (ii) the space hold fee is nonrefundable in the event Tenant declines to exercise the Option to Lease the First Floor Option Space.

2.3.2 PTRP Option

Landlord hereby grants to Tenant the option to lease that 4387 rentable square feet of "PTRP Space" on the first floor of the building as designated on the attached Exhibit A-2 (the "PTRP Option Space"), the exercise of such Option to Lease being conditional on Tenant's exercise of the Renewal Option. Tenant will exercise this Option to Lease, if it elects exercise, by giving written notice to Landlord not less than 180 days prior to Tenant's intended occupancy date for such space (the "PTRP Occupancy Effective Date"); provided that in no event shall the PTRP Occupancy Effective Date be prior to July 31, 2007. Unless Landlord otherwise agrees, Tenant may exercise this Option to Lease only with respect to all of the PTRP Option Space. Exercise of this Option to Lease shall effect a lease of the PTRP Option Space from the PTRP Occupancy Effective Date through the balance of the Renewal Term and the PTRP Option Space shall thereupon become part of the Demised Premises. Tenant will pay

Rent for such PTRP Option Space during the Renewal Term as set forth in paragraphs 3.1 and 3.2.

2.3.3 Second Floor Option

Landlord hereby grants to Tenant the option to lease an additional 20,669 rentable square feet of space, being all of the second floor of the Building (the “Second Floor Option Space”), the exercise of such Option to Lease being conditional on Tenant’s exercise of the Renewal Option. Tenant will exercise this Option to Lease, if it elects exercise, by giving written notice to Landlord not less than twelve (12) months prior to Tenant’s intended occupancy of such space (the “Second Floor Occupancy Effective Date”); provided that in no event shall the Second Floor Occupancy Effective Date be prior to July 31, 2007. Unless Landlord otherwise agrees, Tenant may exercise this Option to Lease only with respect to all of the Second Floor Option Space. Exercise of this Option to Lease shall effect a lease of the Second Floor Option Space from the Second Floor Occupancy Effective Date through the balance of the Renewal Term and the Second Floor Option Space shall thereupon become part of the Demised Premises. Tenant will pay Rent for such Second Floor Option Space during the Renewal Term as set forth in paragraphs 3.1 and 3.2.”

D. By deleting clause “b” of the third sentence of paragraph 2.4, and substituting the following in lieu thereof:

“b) upon Tenant’s request pursuant to paragraph 6.1 to require Landlord to provide Tenant an allowance for redecorating or for upfitting of the Demised Premises, and continuing for the remainder of the Renewal Term; and”

E. By deleting paragraph 3.1 of the Lease and substituting the following in lieu thereof:

“3.1 Tenant will pay annual rental pursuant to the following schedule (“rsf” indicates “rentable square foot”):

| Term | Effective Date | Demised Premises | | | | |
|--------------|---------------------------------------|--------------------------------|----------------------|---------------------------|-------------------------|--------------------|
| | | 40,432 rsf 3rd & 4th Floors | 1000 rsf First Floor | 1st Floor Option Space | 1st Floor PTRP Space | Second Floor Space |
| Initial Term | Commencement Date 8-1-02 | 36.00/rsf | — | — | — | — |
| | Amendment Date 1-1-05 | — | 15.00/rsf | — | — | — |
| | First Floor Occupancy Effective Date | — | — | 15.00/rsf* | — | — |
| Renewal Term | 8-1-2007 | 33.60/rsf | 15.00/rsf | 15.00/rsf* | — | — |
| | PTRP Occupancy Effective Date | — | — | — | 15.00/rsf* | — |
| | Second Floor Occupancy Effective Date | — | — | — | — | 15.00/rsf* |

*if corresponding option is exercised

(herein collectively "Rent"). Rent is payable in equal monthly installments, in advance on the first day of each calendar month of each calendar year during the Initial Term and, if applicable, the Renewal Term, prorated for any partial month. Any increases or decreases in the amount of square footage leased during a month will be adjusted in the subsequent monthly payment. Rent payments shall be payable to "Wake Forest University Health Sciences" and sent to Landlord in care of Controller's Office, Attention: Doug Lischke, Medical Center Boulevard, Winston-Salem, NC, 27157."

F. By deleting the first sentence of paragraph 4.1 of the Lease and substituting the following in lieu thereof:

"Tenant shall have the right, subject to the Landlord's obligations to existing tenants, to the exclusive use (without payment of any additional rent) of a pro rata share of the underground parking available for the Building based on Tenant's rentable square footage; such spaces shall be designated for use by Tenant and are, as of the Commencement Date (and subject to increase upon exercise of any one or more of the Options to Lease set forth in paragraph 2.3), as shown on attached Exhibit A-2."

G. By deleting paragraph 6 of the Lease and substituting the following in lieu thereof:

6. Upfitting/Condition of Demised Premises

6.1 Except as otherwise set forth herein, Tenant accepts the Demised Premises in their present condition, which condition includes certain upfitting and improvements to the third and fourth floors made by Landlord at its cost and expense and to Tenant's specifications prior to the Commencement Date and in accordance with that prior lease agreement between the parties dated April 20, 2001. At any time during the second year of the Renewal Term, Landlord will provide Tenant, upon Tenant's request, an allowance of Ten Dollars (\$10.00) per rentable square foot of the third and fourth floors of the Demised Premises for use by Tenant in redecoration of such floors of the Demised Premises.

6.2 On or before the Amendment Date, Landlord shall have installed at its cost and expense a door, ceiling grid with lights, and one electrical outlet in the 1000 rentable square feet of space from the

first floor of the Building added to the Demised Premises as of the Amendment Date.

- 6.3 Upon Tenant's exercise of the Option to Lease the First Floor Option Space, Landlord will at its cost and expense install up to four card readers and repair carpet and patch and paint as necessary.
- 6.4 Upon Tenant's exercise of the Option to Lease the PTRP Option Space, Landlord will at its cost and expense install two card readers and a door at the hallway off the main lobby.
- 6.5 Upon Tenant's exercise of the Option to Lease the Second Floor Option Space, Landlord will provide Tenant, upon Tenant's request, an allowance of Ten Dollars (\$10.00) per rentable square foot of leased Second Floor Space as an upfit allowance for such Second Floor Space.

3. Except as amended herein, all of the terms and conditions of the Lease shall remain in full force and effect.

IN WITNESS WHEREOF, Landlord and Tenant have caused this Amendment to be executed, pursuant to authority duly granted, effective as of the Amendment Date set forth above.

LANDLORD:

Wake Forest University Health Sciences

By: /s/ Richard H. Dean, M.D.
Richard H. Dean, M.D.
President

Date: January 6, 2005

TENANT:

Targacept, Inc.

By: /s/ J. Donald deBethizy
J. Donald deBethizy
President

Date: January 4, 2005

Exhibit A

Demised Premises

The Demised Premises consists of the following:

- As of the Commencement Date, all of the third and fourth floors, consisting of 40,432 rentable square feet, including within the meaning of “Premises” or “Demised Premises” the entire fourth floor of the Building, to be utilized as Tenant’s laboratory facilities, encompassing 20,216 rentable square feet, and 20,216 rentable square feet of general office space on the third floor.
- As of the Amendment Date, an additional 1,000 rentable square feet on the first floor of the Building, to be utilized as “Tenant’s Storage Space,”

together with rights of use of and subject to the rights of others in and to the Common Areas of the Building. Diagrams of the Demised Premises and Common Areas (such Common Areas designated in blue and in yellow) are as shown on the attached Exhibit A-2.

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" and to the use of our report dated January 22, 2004 (except Note 18 as to which the date is , 2005), in Amendment No. 4 to the Registration Statement (Form S-1 No. 333-115538) and related Prospectus of Targacept, Inc. dated January 20, 2005.

Ernst & Young LLP

Greensboro, North Carolina
January 20, 2005

The forgoing consent is in the form that will be signed upon the completion of the restatement of capital accounts described in Note 18 to the financial statements.

/s/ Ernst & Young LLP

Greensboro, North Carolina
January 20, 2005