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eyetech pharmaceuticals Inc

Biotechnology with a Focus on Eye Disease

2004 Annual Report

"Macugen is among the first treatments to target the underlying biology of wet age-related macular degeneration."

—DR. LESTER M. CRAWFORD, Acting Commissioner of the FDA, www.FDA.gov (FDA News, December 20, 2004)

Corporate *Overview*

Eyetech Pharmaceuticals, Inc. is a biopharmaceutical company that specializes in the development and commercialization of novel therapeutics to treat diseases of the eye. Eyetech's initial focus is on diseases affecting the back of the eye. Eyetech is commercializing and further developing Macugen® (pegaptanib sodium injection) with Pfizer Inc. for the treatment of neovascular (wet) age-related macular degeneration (AMD). Macugen is also being studied for other indications including diabetic macular edema and retinal vein occlusion.

"The FDA's approval of Macugen for all neovascular age-related macular degeneration represents an important paradigm shift in the treatment of this devastating disease. Macugen is a novel treatment based on elegant science that for the first time targets the underlying cause of the disease, which has led to our broad AMD label, including all subtypes and sizes."

—DAVID R. GUYER, M.D., Chief Executive Officer and Co-founder of Eyetech Pharmaceuticals, Inc.

2004 *Milestones*

JANUARY 2004

Eyetech announced the pricing of its initial public offering of 6,500,000 shares of its common stock on January 29th at a price of $21 per share. Eyetech's common stock made its market debut on the Nasdaq Stock Market on January 30th under the symbol "EYET" and closed the first day of trading at $32.40.

MARCH 2004

Eyetech presented detailed data from its pivotal Phase 2/3 clinical trial for neovascular AMD, the VEGF Inhibition Study in Ocular Neovascularization (VISION). Overall results showed that Macugen met its primary efficacy endpoint with high statistical significance, had a favorable safety profile and demonstrated positive patient compliance rates.

(from left to right) Hamed M. Abdou, Ph.D., Senior Vice President, Technical Operations; Joseph T. Kennedy, Acting Chief Legal Officer; David L. Hallal, Senior Director, National Sales; William B. O'Connor, Vice President, Finance; Christopher Carroll, CPA, Chief Accounting Officer; Samir Patel, M.D., Chief, Clinical and Commercial Strategy

"Macugen is the first anti-angiogenic treatment approved in ophthalmology and represents the beginning of a new era. The anti-angiogenic approach specifically addresses, for the first time, an underlying cause of blindness in age-related macular degeneration. Anti-angiogenesis has evolved from theory to therapy."

—JUDAH FOLKMAN, M.D., Julia Andrus Dyckman Professor of Pediatric Surgery at Children's Hospital in Boston and Harvard Medical School

Eyetech and Pfizer announced the completion of the filing of a new drug application (NDA) with the U.S. Food and Drug Administration (FDA) for Macugen.

Eyetech entered into an exclusive agreement with Archemix to collaborate on the research and development of aptamers for use in the treatment of ophthalmic diseases.

MAY 2004

APRIL 2004

Eyetech announced that a Phase 2 study of Macugen showed positive visual and anatomical outcomes for diabetic macular edema (DME) with a well-tolerated safety profile.

JUNE 2004

(from left to right) Emmett T. Cunningham, Jr., M.D., Ph.D., M.P.H., Senior Vice President, Medical Strategy; Pat Barnett, R.N., J.D., Director of Reimbursement and Health Policy; David R. Guyer, M.D., Chief Executive Officer; Glenn P. Sblendorio, Chief Financial Officer; Paul G. Chaney, Chief Operating Officer

"I couldn't see faces. All colors were hideous; trees and grass were a frosted gray. There was a big round spot in the middle of my vision. It scared me to death. I would have gone blind if I hadn't gotten into this study with Dr. Eaton." "It's phenomenal. I can thread a needle. Before Macugen, I could no more have threaded a needle than flown to the moon."

—SEEING, BELIEVING—New Medications for Macular Degeneration Bringing Hope to Patients, *Naples Daily News,* January 27, 2005

AUGUST 2004

Eyetech and Pfizer announced that the complete NDA for Macugen had been accepted by the FDA. The acceptance of the NDA satisfied a milestone provision in the collaboration agreement for a further license fee payment from Pfizer to Eyetech of $10 million.

The FDA's Dermatologic & Ophthalmic Drugs Advisory Committee met to review the clinical submission of Macugen.

SEPTEMBER 2004

Eyetech and Pfizer announced that the European Medicines Agency (EMEA) had accepted the filing of the marketing authorization application for Macugen.

OCTOBER 2004

Eyetech announced that patients benefit from two years of treatment with Macugen for neovascular AMD. The safety profile continued to be favorable, similarly to the first year.

Dear *Stockholders,*

Imagine not being able to see. This is the unfortunate reality for many elderly Americans who suffer from the devastating disease called neovascular age-related macular degeneration, also known as wet AMD.

Prior to co-founding Eyetech Pharmaceuticals, Inc., I spent many years as an academic retinal surgeon, where I was increasingly frustrated by the lack of therapies for these patients, and the little interest then in addressing the disease by big pharmaceutical and biotech companies.

We started Eyetech in 2000, and in only four years we took the company public, received the U.S. Food and Drug Administration's (FDA) approval for our lead product, Macugen® (pegaptanib sodium injection), and, in January 2005, we launched Macugen in the United States market with our partner Pfizer.

Macugen represents a paradigm shift, since it is the first and only drug targeting the underlying cause of the disease and is approved for all neovascular AMD without restrictions.

In December 2004, *The New England Journal of Medicine* published "Pegaptanib for Neovascular Age-Related Macular Degeneration," another sign of the importance of Macugen to the medical community and patients.

"...[The VEGF Inhibition Study in Ocular Neovascularization] marks the start of a new era in the treatment of age-related macular degeneration and other causes of ocular neovascularization." "It is the efficacy of a new medical approach that makes this a landmark study."

—FREDERICK L. FERRIS, M.D., Editorial, *New England Journal of Medicine*, Vol. 351, No. 27, page 2,864, December 30, 2004

2004 was a year of significant progress for Eyetech, as we continued to build a fully integrated biotechnology company. We now have an approved product, our own highly educated and experienced sales force, several near- and long-term product opportunities, a world-class research facility in addition to a potential future second source of manufacturing supply for our product.

After receiving positive results from the pivotal clinical trial of Macugen in neovascular AMD, we filed a new drug application (NDA) with the FDA and received "fast track" priority review under the agency's Pilot 1 program.

In December 2004, we received FDA approval for Macugen for use in all neovascular (wet) age-related macular degeneration—the broadest possible label—enabling us to provide Macugen to the many patients suffering from this devastating disease.

Macugen is the first FDA-approved therapy for the eye that is designed to inhibit angiogenesis, the process by which new blood vessels develop, which is the underlying cause of many back-of-the-eye diseases. The father of anti-angiogenesis research, Professor Judah Folkman, M.D., Julia Andrus Dyckman Professor of Pediatric Surgery at Children's Hospital and Harvard Medical School, said that the approval of Macugen "...represents the beginning of a new era." He went on to say, "The anti-angiogenic approach specifically addresses, for the first time, an underlying cause of blindness in age-related macular degeneration. Anti-angiogenesis has evolved from theory to therapy."

We announced proof of principle Phase 2 data for Macugen in diabetic macular edema (DME), and plan to start a Phase 2/3 trial in 2005. DME is another large unmet medical need market where there is no current FDA-approved drug. We started a Phase 2 clinical trial for

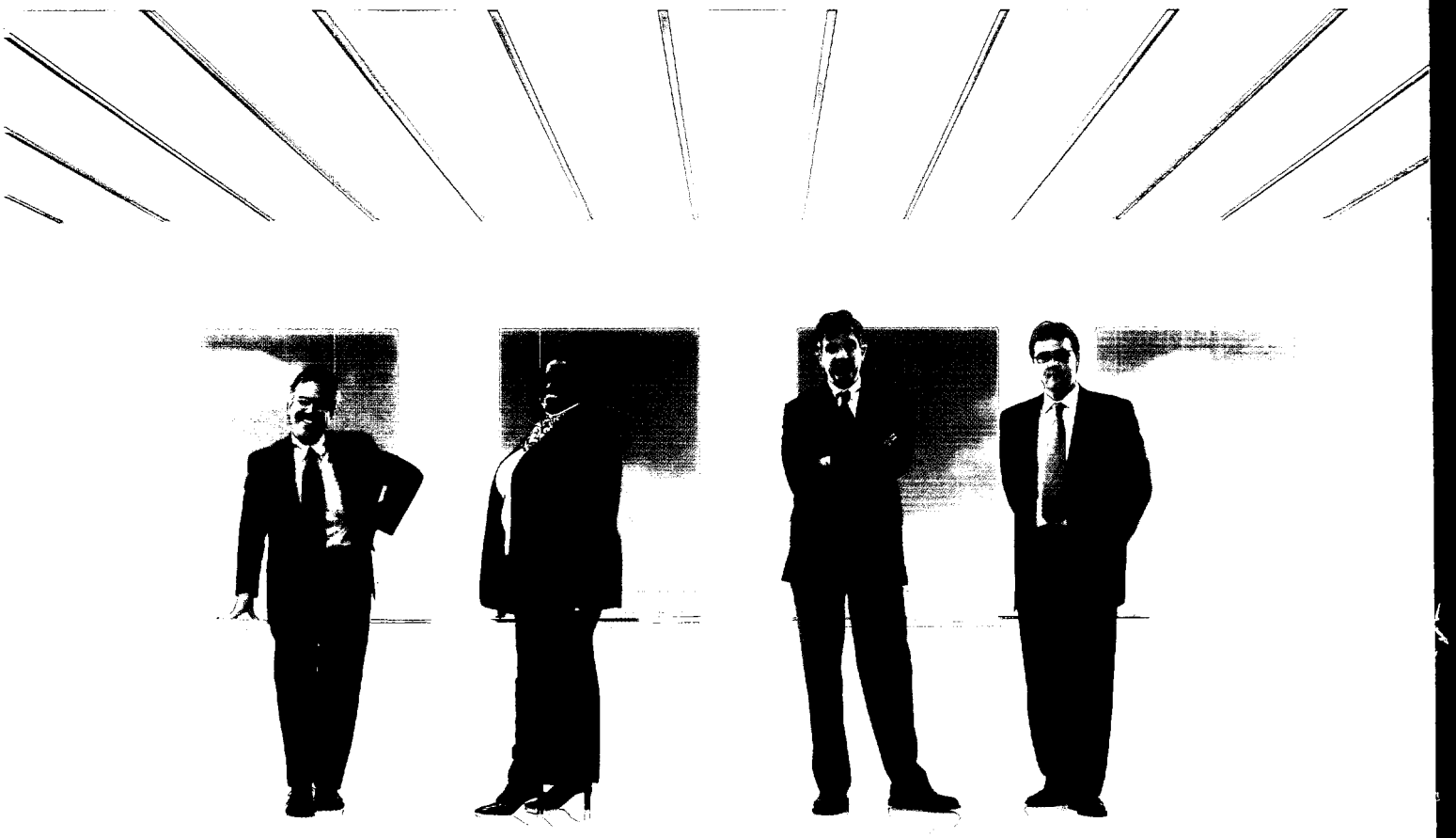
Eyetech and Pfizer received FDA approval for Macugen for all neovascular (wet) AMD—a broad label—including all lesion subtypes and sizes.

Macugen study results were published in the December 30, 2004 issue of *The New England Journal of Medicine*, reflecting the importance of Eyetech's clinical data to the retinal surgeon community.

NOVEMBER 2004

DECEMBER 2004

Eyetech purchased most of the assets of Transgenomic, Inc., an oligonucleotide manufacturing facility located in Boulder, Colorado.



(from left to right) Barrett Katz, M.D., Vice President, Medical Strategy; Evelyn Harrison, Vice President, Clinical Research; Anthony P. Adamis, M.D., Executive Vice President, Research and Development, Chief Scientific Officer; David T. Shima, Ph.D., Senior Vice President, Research and Preclinical Development

"I feel that I've certainly been blessed by it and have another chance to have a life, because I can read. I could not read before."

—MARY COMPSON, interviewed on NBC News, January 31, 2005

the use of Macugen in the treatment of retinal vein occlusion in 2004, where we hope to ultimately obtain regulatory approval for the use of Macugen in this additional large market with an unmet medical need.

The focus of the management team at Eyetech is directed towards the critical activities of the business at hand, as well as long-range planning for growth in the future. We are focusing on the priorities that will allow us to meet our goals while delivering products that have the potential to change the practice of medicine and improve patients' lives. In closing, we continue to manage our business with the intent of delivering breakthrough therapies to patients while building sound and consistent growth, and continuing to increase shareholder value.

We appreciate your continued support and encouragement. We are confident that the team we have built, the science we are conducting, and the partnerships we have established have put us in a strong position to maximize the commercial opportunities for Macugen and drive Eyetech's continued success.

Yours sincerely,

DAVID R. GUYER, M.D., Chief Executive Officer

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

FORM 10-K

(Mark One)

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

For the Fiscal Year Ended December 31, 2004

or

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

For the transition period from to

Commission file number 000-50516

Eyetech Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its Charter)

Delaware	**13-4104684**
(State of incorporation)	*(I.R.S. Employer Identification No.)*

3 Times Square, 12th Floor
New York, New York 10036
(Address of principal executive offices) (Zip Code)

(212) 824-3100
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Securities Exchange Act of 1934:
None

Securities registered pursuant to Section 12(g) of the Securities Exchange Act of 1934:
Common Stock, Par Value $0.01 Per Share
(Title of class)

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

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

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b-2). Yes ☐ No ☑

Aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last sale price for such stock on June 30, 2004 (the last business day of the registrant's most recently completed second fiscal quarter: $1,480,652,143.

The number of shares of registrant's common stock outstanding on March 10, 2005 was 42,989,062.

Portions of the registrant's Definitive Proxy Statement for the 2005 Annual Meeting of Stockholders of the registrant to be held May 11, 2005 are incorporated by reference into Part III of this Form 10-K.

TABLE OF CONTENTS

PART I

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements relating to future events and our future performance within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Stockholders are cautioned that such statements involve risks and uncertainties. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's beliefs and assumptions. All statements, other than statements of historical facts, included in this report regarding our strategy, future operations, future clinical trials, future financial position, future sales, future revenues, future profitability, projected costs, prospects, plans and objectives of management are forward-looking statements. The words "anticipates," "believes," "estimates," "expects," "intends," "may," "plans," "projects," "will," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this report, particularly in the "Risk Factors that May Affect Results" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make. We do not assume any obligation to update any forward-looking statements.

Item 1. *Business*

Overview

Eyetech Pharmaceuticals, Inc. is a biopharmaceutical company that specializes in the development and commercialization of novel therapeutics to treat diseases of the eye. Our initial focus is on diseases affecting the back of the eye, particularly the retina, because we believe that these diseases have the greatest unmet medical need and represent the largest potential market opportunities in ophthalmology.

In January 2005, we began selling our first product, Macugen® (pegaptanib sodium injection), in the United States for use in the treatment of all types of neovascular age-related macular degeneration, known as wet AMD or neovascular AMD. Macugen was approved in December 2004 by the United States Food and Drug Administration, or FDA, to treat neovascular AMD under its "fast track," Pilot 1 program, which is reserved for drug candidates that may meet a significant unmet medical need. We are also developing Macugen for the treatment of diabetic macular edema, known as DME, and retinal vein occlusion, known as RVO. In December 2002, we entered into a collaboration with Pfizer Inc. to develop and commercialize Macugen for the prevention and treatment of diseases of the eye.

Macugen is the first and only FDA-approved therapy for the treatment of all subtypes of neovascular AMD. Macugen addresses the abnormal blood vessel growth and blood vessel leakage that is believed to be the underlying cause of the disease. We believe Macugen has benefits over existing therapies in the treatment of neovascular AMD. We also believe Macugen may provide considerable benefits over the existing therapies for the blood vessel leakage associated with DME. Significant scientific evidence suggests that the presence in the eye of elevated levels of a protein known as vascular endothelial growth factor, or VEGF, plays an important role in causing this abnormal blood vessel growth and blood vessel leakage. Based on animal tests that we conducted, we believe that Macugen prevents VEGF from binding to its natural receptor, thereby inhibiting such abnormal blood vessel growth and blood vessel leakage.

Neovascular AMD and DME are two of the leading causes of severe vision loss and blindness in the adult population. In the United States, we estimate that as many as 15 million people suffer from some form of AMD and that there are more than 1.6 million cases of neovascular AMD. Approximately 500,000 new cases of neovascular AMD arise each year world-wide, approximately 200,000 of which in the United States.

Although neovascular AMD represents approximately 10% of all AMD cases, it is responsible for up to 90% of the severe vision loss associated with AMD, with a majority of neovascular AMD patients experiencing severe vision loss in the affected eye within months to two years after diagnosis of the disease. Because AMD generally affects adults over 50 years of age, we expect the incidence of AMD to increase significantly as the baby boom generation ages and overall life expectancy increases.

In May 2004, we announced preliminary data from our Phase 2 clinical trial for the use of Macugen in the treatment of DME, showing positive visual and anatomical outcomes. The FDA has also given "fast track" designation to Macugen for the treatment of DME. Diabetic retinopathy is the leading cause of blindness in people less than 50 years of age in developed countries. DME is a manifestation of diabetic retinopathy and the leading cause of vision loss in diabetic retinopathy. In the United States, there are approximately 500,000 people suffering from DME, with approximately 75,000 new cases each year. We expect the incidence of DME in the United States to increase as the number of people with diabetes increases. We believe that the prevalence and incidence of AMD and DME in the European Union are similar to those in the United States. Because the existing treatments for DME have significant limitations, there is a significant unmet medical need for a new therapy for this disease.

As part of our collaboration with Pfizer, we and Pfizer are co-promoting Macugen in the United States and are further developing Macugen. We have granted Pfizer the exclusive right to develop and commercialize Macugen outside the United States under a royalty-bearing license. Pfizer has filed new drug applications for Macugen with the European Medicines Agency, which covers 25 countries, and an additional six countries. Under the collaboration, we also are entitled to participate in the United States in detailing Pfizer's product Xalatan for the treatment of glaucoma.

We are led by a team of experienced pharmaceutical industry executives and recognized experts in ophthalmology and vision research. We believe that this team provides us with a significant complement of capabilities in the discovery, development and commercialization of novel therapeutics to treat diseases of the eye.

Eyetech Pharmaceuticals, Inc. is a Delaware corporation formed in February 2000.

Our Business Strategy

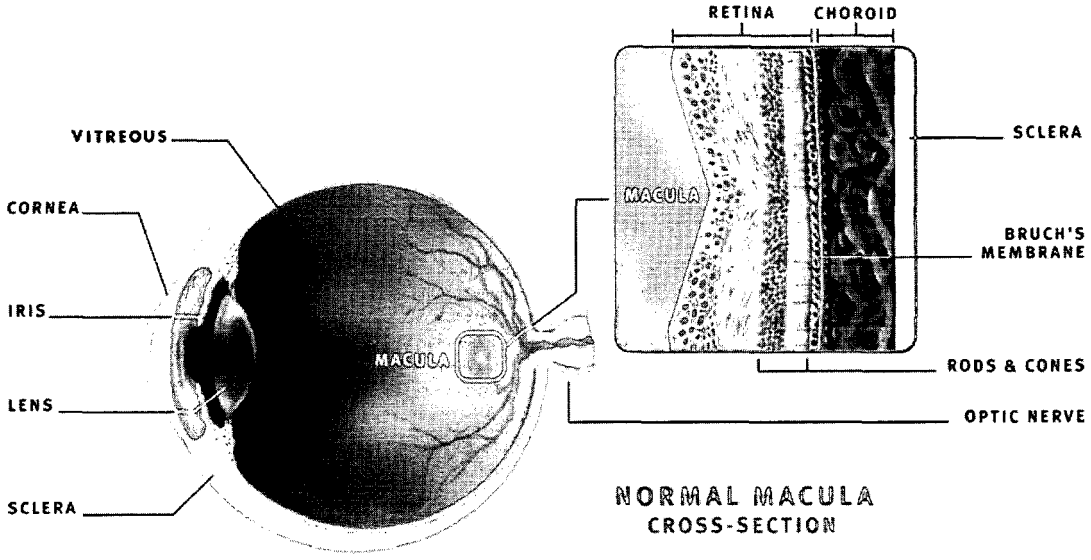
Our mission is to develop and commercialize novel therapeutics to treat diseases of the eye, with an initial focus on diseases of the back of the eye. The key elements of our strategy in support of this mission are to:

- *Maximize Commercial Potential of Macugen.* We are devoting most of our efforts to commercializing Macugen in the United States for the treatment of neovascular AMD and completing the clinical and regulatory development of Macugen. We are exploring the application of Macugen to additional ophthalmic indications, including DME and RVO.
- *Develop Alternative Drug Delivery Technologies.* We are working to develop or acquire alternative technologies for the administration of drugs to the back of the eye that could facilitate the use of Macugen and other drugs as continuing or even preventive treatments for various back of the eye diseases, including neovascular AMD, DME and RVO.
- *Identify New Ophthalmic Products.* We have established an internal research effort with the goal of discovering and validating new ophthalmic disease targets and developing novel therapeutics for the treatment of ophthalmic diseases. In particular, we are actively engaged in the pre-clinical development of compounds to be used in combination with Macugen that may enhance its effectiveness, or expand its clinical utility. We are also seeking to license or otherwise acquire the rights to potential new drugs and drug targets for the treatment of ophthalmic disease. We have an agreement with Archemix Corp. to collaborate on the research and development of aptamers for ophthalmic indications. Aptamers are single strands of oligonucleotide that bind to molecular targets in a manner conceptually similar to antibodies. As such, aptamers have a number of desirable characteristics for use as therapeutics, including biological efficacy, high specificity and affinity, and excellent pharmacokinetic properties.

- *Explore Additional Non-Ophthalmic Indications for Macugen.* We are evaluating whether the anti-VEGF characteristics of Macugen may make it an attractive local treatment for cancer. For indications outside of ophthalmology, we may seek collaborators or licensees for drug development and commercialization.

Eye Disease

The human eye possesses focusing elements in the front, the cornea and lens, and a light-sensing element in the back, the retina. Light falls on the photoreceptors that are part of the retina, called rods and cones, and is converted into electrical energy, which travels via the optic nerve to the brain. The central most portion of the retina is the macula, which is the region responsible for seeing color and the acute central vision necessary for activities such as reading, face recognition, watching television and driving. The brain processes the complex signals sent from the retina into vision. The following diagram illustrates the principal elements of the anatomy of a healthy eye, including a detailed cross-section of the back of the eye.



Eye disease can be caused by many factors and can affect both the front and back of the eye. In its most extreme cases, eye disease can result in either partial or total blindness. In the developed world, the major diseases that result in blindness are those affecting the retina, including AMD, diabetic retinopathy, of which DME is a manifestation, and glaucoma. These diseases deny patients of their sight, and, as a result, their ability to live independently and perform daily activities.

Age-Related Macular Degeneration

AMD is a chronic, progressive disease of the macula that results in the loss of central vision. The most common symptoms are a central blurred or blank spot, distortion of objects or simply blurred vision. Peripheral vision usually remains intact. The disease typically affects patients initially in one eye, with a high likelihood of it occurring in the second eye over time. Because AMD is strongly correlated with aging, we believe that it is likely for the disease to recur, notwithstanding treatment, as the aging process continues. Thus, patients who have been administered the existing therapies for AMD have frequently required retreatment.

According to the Macula Vision Research Foundation, as many as 15 million people in the United States suffer from some form of AMD, with more than 1.6 million experiencing the active blood vessel growth and blood vessel leakage associated with neovascular AMD. In addition, AMD Alliance International reports that

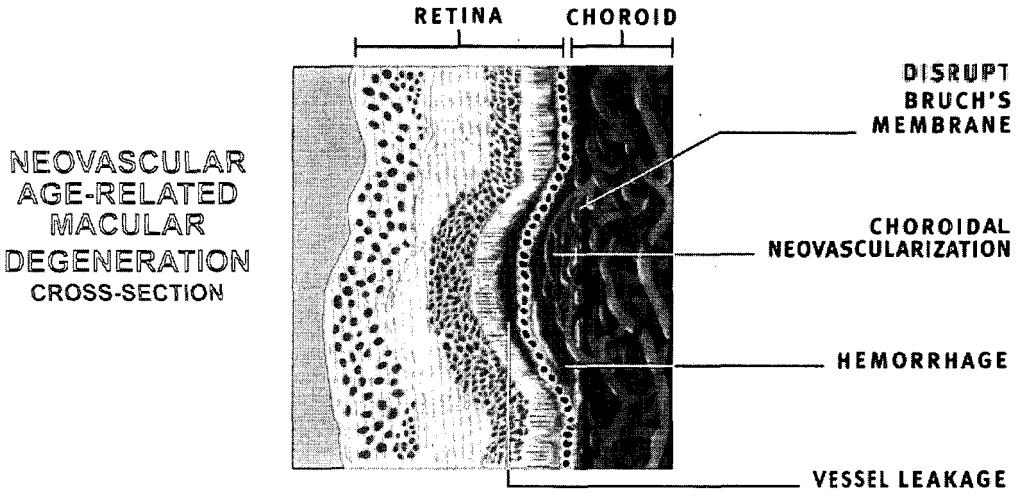
approximately 500,000 new cases of neovascular AMD arise each year world-wide, including approximately 200,000 new cases of neovascular AMD each year in the United States. According to the Centers for Disease Control and Prevention, or CDC, the rate of AMD increases sharply with age, from 18% among people 70 to 74 years of age to 47% among people 85 years and older. According to the U.S. Census Bureau, the number of people in the United States aged 50 or older is approximately 80 million and is expected to increase by approximately 40% over the next two decades. We expect that this increase in the number of elderly people will result in a significant increase in the number of cases of AMD in the United States. Further, as patients lose their sight to neovascular AMD, and thereby lose their ability to perform the routine functions of daily living, up to one-third of such patients become clinically depressed. We believe this further underscores the need for treatment for neovascular AMD.

There are two forms of AMD, "dry" AMD and "wet" or "neovascular" AMD:

- *Dry AMD.* Dry AMD is the most common form of AMD, representing approximately 90% of all cases. However, dry AMD accounts for only 10% of the severe vision loss associated with AMD. Dry AMD is characterized by the development of yellow-white deposits under the retina, known as drusen, and sometimes the deterioration of the retina, although without abnormal blood vessel growth and bleeding. There is no generally accepted treatment for dry AMD, although vitamins, antioxidants and zinc supplements may slow its progression. Over time, dry AMD cases often develop into neovascular AMD.

- *Neovascular AMD.* Neovascular AMD represents approximately 10% of all cases of AMD, but is responsible for up to 90% of the severe vision loss associated with the disease. Neovascular AMD occurs when new blood vessels from the tissue layer in the eye just beneath the retina, called the choroid, invade into the retinal layers through a membrane known as Bruch's membrane. This abnormal blood vessel growth generally is known as angiogenesis and, in the context of neovascular AMD, is called choroidal neovascularization. These new blood vessels tend to be fragile and often bleed and leak fluid into the macula, resulting in loss of vision. For this reason, neovascular AMD is also known as wet AMD. Untreated, this blood vessel growth and leakage can lead to scarring and, eventually, to the destruction of the macula. The majority of patients with neovascular AMD experience severe vision loss in the affected eye within months to two years after diagnosis of the disease.

The following diagram is a detailed cross-section of the back of the eye as affected by neovascular AMD.



The abnormal blood vessel growth of neovascular AMD can be located either directly under the area at the center of the macula, known as the fovea, or away from the fovea. Neovascular AMD that occurs directly under the fovea is known as subfoveal neovascular AMD. Neovascular AMD that occurs elsewhere in the

macula is known as either extrafoveal or juxtafoveal neovascular AMD. The fovea is responsible for the ability to see fine detail and color. More than 90% of neovascular AMD cases are subfoveal.

Subfoveal neovascular AMD is divided into three principal subtypes based on the pattern of the abnormal blood vessels, or lesions, as seen in the retina through an imaging procedure known as angiography. The classic pattern consists of well-defined abnormal blood vessels with distinct edges. In the occult pattern, the edges of the abnormal blood vessels are more poorly demarcated and diffuse. The principal subtypes of subfoveal neovascular AMD, based on the patterns of the abnormal blood vessels, are the following:

- *Predominantly Classic.* In the predominantly classic subtype, more than 50% of the patient's abnormal blood vessels are of the classic pattern. We estimate that this subtype accounts for up to 25% of the cases of subfoveal neovascular AMD and generally has the most aggressive disease pathology, leading to more rapid vision loss than the other subtypes.
- *Minimally Classic.* In the minimally classic subtype, fewer than 50% of the patient's abnormal blood vessels are of the classic pattern. We estimate that this subtype accounts for approximately 35% of the cases of subfoveal neovascular AMD and generally has a less rapid rate of vision loss than the predominantly classic subtype, but a more rapid rate than the occult subtype.
- *Occult.* In the occult subtype, all of the patient's abnormal blood vessels are of the occult pattern. We estimate that this subtype accounts for approximately 40% of the cases of subfoveal neovascular AMD and generally has a less rapid rate of vision loss.

We based the foregoing estimates of the percentages of patients suffering from each subtype on a survey of ophthalmologists that we conducted in 2002. These estimates are supported by the enrollment data from our Phase 2/3 pivotal clinical trials for neovascular AMD.

In the United States, Macugen is the first and only FDA-approved drug for all subtypes of neovascular AMD. One other therapy is FDA-approved in the United States for the predominantly classic subtype of neovascular AMD. In the European Union, there is an approved therapy for only the predominantly classic and occult subtypes. As a result, prior to the approval of Macugen, we estimate that the previously approved therapies are only indicated for up to 25% of United States patients and 65% of European patients, thus leaving a significant unmet medical need for the balance.

Diabetic Macular Edema

DME is a complication of diabetic retinopathy, a disease affecting the blood vessels of the retina. Diabetic retinopathy results in multiple abnormalities in the retina, including retinal thickening and edema, hemorrhages, impeded blood flow, excessive leakage of fluid from blood vessels and, in the final stages, abnormal blood vessel growth. This blood vessel growth can lead to large hemorrhages and severe retinal damage. When the blood vessel leakage of diabetic retinopathy causes swelling in the macula, it is referred to as DME. The principal symptom of DME is a loss of central vision. Risk factors associated with DME include poorly controlled blood glucose levels, high blood pressure, abnormal kidney function causing fluid retention, high cholesterol levels and other general systemic factors.

According to the World Health Organization, diabetic retinopathy is the leading cause of blindness in working age adults and a leading cause of vision loss in diabetics. The American Diabetes Association reports that there are approximately 18 million diabetics in the United States and approximately 1.3 million newly diagnosed cases of diabetes in the United States each year. Prevent Blindness America and the National Eye Institute estimate that in the United States there are over 5.3 million people aged 18 or older with diabetic retinopathy, including approximately 500,000 with DME. The CDC estimates that there are approximately 75,000 new cases of DME in the United States each year.

Limitations of Other Available Therapies for Neovascular AMD

Other than Macugen, the therapies currently available for the treatment of neovascular AMD are photodynamic therapy and thermal laser treatment.

Photodynamic Therapy. Photodynamic therapy involves the use of a light-activated drug, or photosensitizer, named Visudyne® to treat neovascular AMD. The therapy involves a two-step process in which the drug is administered systemically by intravenous infusion and then a dose of low energy light is delivered to the target site to activate the photosensitizer and destroy the newly grown abnormal blood vessels. Worldwide sales of Visudyne in 2004 were approximately $448 million.

Visudyne therapy has an important therapeutic indication limitation in that it is approved in the United States only for the treatment of the predominantly classic subtype of subfoveal neovascular AMD, which is estimated to be up to 25% of the total subfoveal neovascular AMD market in the United States. In the European Union, Visudyne therapy is only approved for the treatment of the predominantly classic and occult subtypes of subfoveal neovascular AMD. In April 2004, the Centers for Medicare & Medicaid Services implemented its decision to expand reimbursement for Visudyne therapy to include coverage for its use in the treatment of the minimally classic and occult subtypes, but only for patients in whom the lesions are small and when there is evidence of progression within the three months prior to initial treatment. For this purpose, small lesions are those of less than four disc areas. However, in October 2004, data released from an ongoing Phase III clinical trial to determine if photodynamic therapy with Visudyne can reduce the risk of vision loss in AMD patients with the subfoveal occult subtype with no classic choroidal neovascularization failed to achieve statistical significance at the 12-month time point, one of the trial's primary endpoints.

Visudyne therapy also has a number of clinical shortcomings, including side effects that include the following:

- Severe vision decrease of four lines or more within seven days of treatment reported in 1-5% of patients, subject to partial subsequent recovery in some patients;
- Photosensitivity in the form of skin sunburn following exposure to sunlight; and
- Back pain resulting primarily from the infusion.

In the pivotal clinical trial of Visudyne, approximately 91% of the patients who received Visudyne for the treatment of neovascular AMD experienced a recurrence of the condition within three months of treatment, necessitating retreatment. Furthermore, the method of administering this therapy requires the physician to invest in expensive laser equipment and retain paramedical personnel to assist in the intravenous infusion of the photosensitizer.

Thermal Laser Treatment. Thermal laser treatment, also known as photocoagulation, for the treatment of neovascular AMD entails the use of a high-energy laser to destroy the abnormal blood vessels that are growing and leaking in the macula. This is a surgical procedure and is not subject to FDA approval. Because the lasered portions of the retina are irreversibly destroyed, thermal laser treatment generally is used only for the minority of neovascular AMD patients with the extrafoveal and juxtafoveal forms of the disease, in which the abnormal blood vessel growth and vessel leakage occur away from the center of the macula. Thermal laser treatment is generally not used for subfoveal neovascular AMD because of the risk of immediate and permanent vision loss resulting from the laser burns to the center of the macula. Approximately 50% of the patients who receive thermal laser therapy for the treatment of neovascular AMD experience recurrence of the condition during the ensuing year as a result of regrowth of the abnormal blood vessels. In addition, patients treated with thermal laser therapy frequently experience blind spots, known as scotomas, as a result of the destruction of the area of the retina where the treatment is administered.

Limitations of Currently Available Therapies for DME

There is no approved drug therapy for DME in the United States or the European Union. The current therapies for the treatment of DME are thermal laser treatment and steroid treatment administered by physicians on an off-label basis.

Thermal Laser Treatment. Thermal laser treatment does not result in an improvement in vision in most patients, and some patients continue to lose vision. As discussed above, thermal laser treatment results in focused, localized destruction of portions of the retina. As a result, patients treated with this procedure frequently experience scotomas.

Steroid Therapy. Some physicians recently have begun to treat DME on an off-label basis with injections of corticosteroids into the vitreous, the jelly-like fluid that fills the back of the eye. This method of administering drugs to the back of the eye is known as intravitreal injection. The efficacy of steroid therapy for DME is unknown. Based on the product labels for steroids and numerous published studies, we believe that steroid therapy for DME may have a number of significant side effects that can lead to loss of vision, including worsening of cataracts and steroid-induced glaucoma. The steroids typically used for this treatment are off-patent and inexpensive.

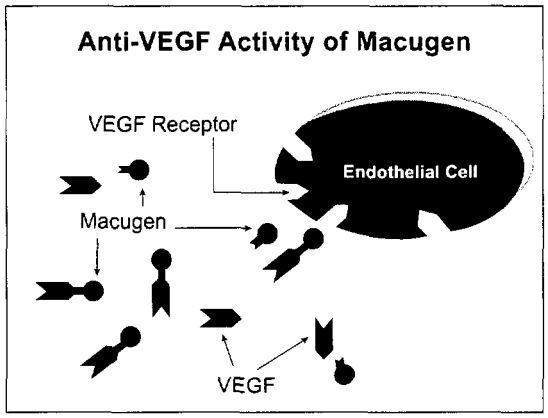
Macugen

Macugen is the first and only FDA-approved therapy for the treatment of all types of neovascular AMD, without angiographic or demographic restrictions. We believe Macugen is a novel, breakthrough therapy for the treatment of neovascular AMD. Macugen addresses the abnormal blood vessel growth and blood vessel leakage that is believed to be the underlying cause of the disease. We believe Macugen has benefits over existing therapies for neovascular AMD. We also believe Macugen may be a novel therapy for the treatment of DME. Based on research regarding the pathologies of neovascular AMD and DME, our knowledge of the mechanism of action of Macugen and the molecular and clinical attributes of this product, we believe that Macugen will overcome many of the limitations of the existing therapies for neovascular AMD and DME.

Mechanism of Action

The active pharmaceutical ingredient in Macugen is a PEGylated aptamer that binds to and inhibits the function of VEGF. An aptamer is a single strand of oligonucleotide that binds with specificity to a particular target, such as VEGF. VEGF is a protein that has been shown to play an important role in the abnormal blood vessel growth and blood vessel leakage associated with neovascular AMD and the blood vessel leakage associated with DME. In multiple preclinical studies in animals, VEGF has been shown to be associated with blood vessel growth and leakage in the eye. In addition, in numerous animal species, anti-VEGF agents have inhibited blood vessel formation and leakage in multiple blood vessel layers of the eye, including the iris, the retina and the choroid. In substantial human clinical research, VEGF concentrations in eyes afflicted with neovascular AMD or DME were found to correlate with the presence and severity of these diseases.

The following diagram illustrates how we believe VEGF is blocked from binding with its natural receptor after Macugen binds with VEGF.



Method of Administration

Macugen is currently administered by intravitreal injection. Before a physician administers the injection of Macugen, the patient receives a pre-injection preparation consisting of a broad-spectrum antibiotic and/or iodine-based topical anti-bacterial followed by topical numbing drops and/or a superficial pre-injection of a local anesthetic to numb the eye. This procedure can be administered by a skilled clinician and can be completed in a typical office visit or other outpatient setting. By injecting this medication into the vitreous, the physician delivers Macugen directly to the affected eye tissue. Intravitreal injections are commonly used in many other therapies for eye disorders, including antibiotic and steroid therapies.

Specificity

In humans, there are at least five subtypes, or isoforms, of VEGF. Based on preclinical *in vitro* and animal studies that we have conducted, we believe that two of these VEGF isoforms, isoforms 165 and 121, are present in the eye in meaningful levels. In these studies, elevated levels of the animal counterpart of human isoform 165 was required for abnormal blood vessel growth in the retina. We believe that the unique shape of the Macugen aptamer allows it to bind to VEGF isoform 165 with high specificity through a lock and key type mechanism. In multiple animal models of pathological ocular vessel growth and leakage, we found that the animal counterpart of VEGF isoform 165 was specifically increased in animals with these conditions. In these tests, we also found that Macugen binding with the animal counterpart of isoform 165 was highly effective in inhibiting abnormal blood vessel growth in the retina. Macugen did not bind with the animal counterpart of isoform 121 to any significant degree. In an animal study conducted by us involving a direct comparison with a VEGF inhibitor that blocks all isoforms, Macugen was as effective at inhibiting abnormal blood vessel growth in the retina as the other VEGF inhibitor. Conversely, in these tests, Macugen did not affect the normal vessels of the retina whereas the pan-VEGF isoform inhibitor altered their growth and survival.

Anti-permeability

VEGF is a very strong inducer of blood vessel permeability. For example, in animal tests VEGF has been shown to be 50,000 times more potent than histamine, the molecule commonly associated with blood vessel leakage related to allergies. Also in animal tests, it has been shown that VEGF is required for the blood vessel permeability associated with neovascular AMD and diabetic retinopathy. In addition to its anti-angiogenic property of inhibiting abnormal blood vessel growth, Macugen has been shown in animal tests to inhibit blood vessels from leaking into the retina. By preventing blood vessel leakage as well as abnormal blood vessel growth, Macugen offers a potential two-pronged approach to the treatment of neovascular AMD. By preventing blood vessel leakage, Macugen also offers a potential treatment for DME. In animal models of diabetes-related blood vessel leakage, the animal counterpart of 165 was specifically increased in the retina. This is the isoform that is selectively inhibited by Macugen in animal models.

No Observed Immunogenicity

Aptamers in general tend not to trigger adverse immune responses. To date, we have not observed any meaningful clinical immunologic reactions to Macugen.

Stability and Attractive Pharmacokinetic Profile

Macugen is a PEGylated molecule, which means that a molecule of polyethylene glycol is attached to the strand of nucleic acid. This PEGylation increases the half-life of the product, which in turn increases the time that Macugen actively targets the disease site. This may allow for less frequent dosing. The unPEGylated Macugen aptamer also demonstrates high stability under various temperature and pH levels, which suggests that the aptamer may be suitable for administration via different delivery methods.

Clinical Development of Macugen

We have completed two years of our Phase 2/3 pivotal clinical trials for the use of Macugen in the treatment of neovascular AMD. These Phase 2/3 clinical trials are ongoing to generate long-term safety data for up to five years. We also completed a Phase 2 clinical trial of Macugen in the treatment of DME. A Phase 2 clinical trial of Macugen in the treatment of RVO is ongoing and open to enrollment.

We are planning to conduct a number of additional clinical trials of Macugen, including a Phase 4 clinical trial for the efficacy of Macugen in combination with Visudyne in the treatment of neovascular AMD, a Phase 4 clinical trial to explore the safety and efficacy of the FDA approved 0.3 mg dose of Macugen versus two additional lower doses of Macugen in patients with neovascular AMD, and a Phase 2/3 clinical trial for the use of Macugen in the treatment of DME. The following table summarizes our material ongoing and planned clinical trials of Macugen.

Indication	Trial Name	Phase	Objectives	Geography	First Patient Enrolled	Number of Patients	Enrollment Status
AMD	EOP 1003	2/3 (Pivotal)	Safety Dose finding Efficacy	International (including U.S.)	October 2001	612	Year two complete; continuation safety study ongoing
	EOP 1004	2/3 (Pivotal)	Safety Dose finding Efficacy	North America	August 2001	578	Year two complete; continuation safety study ongoing
	EOP 1006	2	Pharmacokinetics Safety Efficacy	North America	January 2003	147	Fully enrolled
	EOP 1012	4	Efficacy in combination with Visudyne	International	Planned for the second quarter of 2005	360-380	Planned
	EOP 1014	4	Post-approval FDA commitment Safety Efficacy	International	Planned for the first quarter of 2006	240	Planned
DME	EOP 1005	2	Dose finding Safety Proof of Concept	International (including U.S.)	October 2002	169	Study completed
	EOP 1013	2/3	Dose finding Efficacy	International	Planned for the second half of 2005	Pending	Planned
Retinal Vein Occlusion	EOP 1011	2	Safety Dose finding Proof of Concept	International	May 2004	Planned 90	Currently enrolling

Clinical Trials for the Treatment of Neovascular AMD

Phase 2/3 Pivotal Clinical Trials

Trial Design. In 2001, we initiated two Phase 2/3 pivotal clinical trials for the use of Macugen in the treatment of neovascular AMD. We are conducting one of these trials in North America and one primarily outside North America. We have enrolled 578 patients in the North American trial and 612 patients in the international trial. Retinal specialists at 117 leading medical centers are participating in these two Phase 2/3 clinical trials.

We designed the enrollment criteria for the trials to assess the treatment effect of Macugen in a broad patient population. Both trials enrolled patients with subfoveal neovascular AMD of all three lesion subtypes, with a wide range of lesion sizes and with a variety of other lesion characteristics. Patients who had previously

received subfoveal thermal laser therapy or who had significant subfoveal scarring or atrophy were not eligible to participate in the trials.

Prior to enrollment in the studies, we measured each patient's visual acuity to establish a baseline. Patients with a broad range of baseline visual acuity were included in both trials. To qualify for enrollment, the visual acuity in the patient's study eye had to be between 20/40 and 20/320. Visual acuity in the patient's other eye had to be better than or equal to 20/800. In these trials, visual acuity is measured as the number of letters that the patient can read on the Early Treatment Diabetic Retinopathy Study, or ETDRS, eye chart. This is the standard eye chart used in these types of trials. Five letters on the ETDRS eye chart equates to one line of visual acuity.

To ensure that uniform criteria were applied in characterizing patients' lesions, we engaged the Wilmer Technology Assessment Program, part of the Wilmer Eye Institute at Johns Hopkins University School of Medicine, to review the angiogram of each patient's affected eye. Through the use of this centralized reading center, we were able to confirm patient eligibility and properly classify patients by neovascular AMD subtype before enrolling them in the study.

In these pivotal trials, we randomly assigned patients to one of four groups. Three groups were treated with an intravitreal injection of Macugen. The fourth group served as the control group and received a sham injection. In the first 54 weeks of the trials, the three treated groups received different doses of Macugen: 0.3 mg per injection, 1 mg per injection or 3 mg per injection. To reduce potential bias, both trials use a double-masked study design so that neither the patient nor the investigational staff involved with assessing the vision of the patient knows to which group each patient belongs. The sham injection included all steps involved in the intravitreal treatment injections with the exception that patients in the control group had an empty syringe pressed against their eye walls without a needle. This procedure mimics an intravitreal injection and helps to maintain proper masking. Patients received a treatment every six weeks during the first 54 weeks. At the discretion of the treating physician, patients with predominantly classic subfoveal neovascular AMD who were eligible for photodynamic therapy could receive Visudyne treatment before enrollment on up to one occasion between 8 and 13 weeks prior to enrollment, at baseline and during the trials. In this sense, the control group used in these studies represents usual care and is substantively different from previously published studies in which control groups did not receive treatment.

In North America, we are conducting the trials ourselves. We have engaged a clinical research organization to conduct the clinical trials in Europe, South America, Australia and Israel.

First-Year Clinical Trial Results. Of the 1,208 patients who were enrolled in these trials, the 1,186 patients who received at least one injection and were tested for changes in visual acuity constituted the intent-to-treat population for purposes of analysis of efficacy data. The two trials are scheduled to continue for 154 weeks. However, the primary efficacy endpoint was based on this intent-to-treat patient population at 54 weeks. The following table describes the combined safety patient populations from the two trials.

	Treated with Macugen	Control
Number of patients	892	298
Male/Female(%)	42/58	40/60
Average age at baseline	76.0	75.7
Mean baseline visual acuity score (letters):		
Treated eye	51.5	52.7
Non-treated eye	55.6	57.1
Neovascular AMD subtype(%):		
Predominantly classic	26.0	26.0
Minimally classic	36.0	34.0
Occult	38.0	40.0

Patient characteristics such as gender, age and baseline vision were balanced across the treatment and control groups. Patients also were randomized to establish balanced representation of each subtype of subfoveal neovascular AMD across the treatment and control groups.

There was a high compliance rate in the first 54 weeks of these trials. For the patients who had at least one study treatment, the combined average number of treatments for trial participants was approximately 8.5 out of 9 possible treatments. Further, the completion rate across both trials was also high, with over 90% of all patients remaining in the trials for the full 54 weeks.

Primary Efficacy Endpoint. The primary efficacy endpoint in these trials was the proportion of patients losing less than 15 letters, or three lines, of visual acuity on the ETDRS eye chart from baseline after 54 weeks. This is the same primary clinical endpoint that was used in the pivotal clinical trials for Visudyne. We discussed our trial protocols and statistical analysis plan with the FDA prior to unmasking the data.

Based on our analysis of the data from the combined patient populations of both trials, the primary efficacy endpoint was met with statistical significance for all three doses of Macugen. In connection with our analysis of the combined patient data, we determined statistical significance based on a widely used, conventional statistical method that establishes the p-value of clinical results. Under this method, a p-value of 0.05 or less represents statistical significance. The following table summarizes the combined trial results.

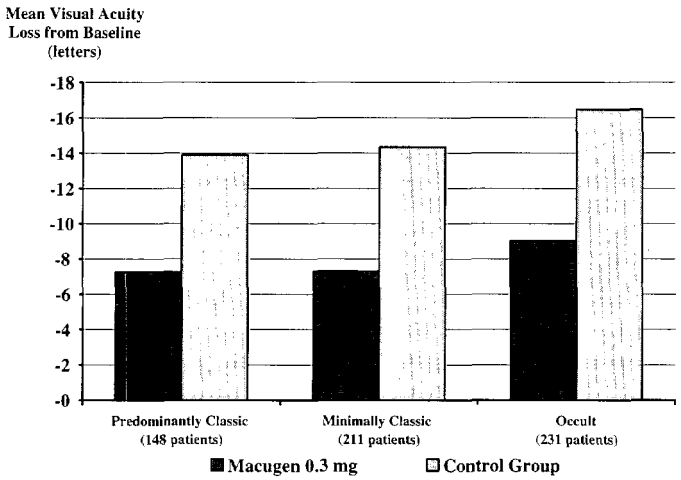
	Patients Losing Less Than 15 Letters		
Dose	Individuals	Percentage	p-value
0.3 mg Macugen	206/294	70%	0.0001
1 mg Macugen	213/300	71%	0.0003
3 mg Macugen	193/296	65%	0.0310
Control	164/296	55%	—

Based on the data from the combined patient populations of both trials, the 0.3 mg dose of Macugen was the lowest effective dose of the three doses tested. On a combined basis, 70% of the patients treated with the 0.3 mg dose of Macugen lost fewer than 15 letters of visual acuity at 54 weeks compared to 55% of the patients in the control group, resulting in a relative difference of 27% between the treated and the control groups. This result had a p-value of 0.0001. In addition, based on our preliminary analysis of the safety data from these trials, each of the three dose levels tested in the trials appears to have a favorable safety profile. To address statistical and other regulatory requirements, we sought and received approval for the 0.3 mg dose of Macugen for the treatment of neovascular AMD.

To qualify for FDA approval, a drug candidate typically has to demonstrate a clinically relevant treatment effect with statistical significance in replicate trials. Moreover, when multiple doses of a drug are tested against a single control group, a more stringent statistical method that accounts for multiple comparisons must be applied. For this purpose, we used the Hochberg multiple comparison procedure. Under the Hochberg procedure, in order to demonstrate statistical significance for any particular dose, it is necessary to establish a p-value that meets a stricter standard than the conventional standard of a p-value of 0.05 or less. We designed our two separate, but substantially identical, North American and international clinical trials to meet these regulatory requirements. For the 0.3 mg Macugen dose, the primary clinical endpoint was achieved with statistical significance in both the North American and international trials using the more stringent Hochberg statistical methodology. The p-value was 0.003 in the North American trial and 0.011 in the international trial.

Efficacy Across All Neovascular AMD Subtypes. The combined data from the two trials demonstrate that the treatment effect of Macugen is consistent across all three subtypes of subfoveal neovascular AMD with respect to both mean vision loss and prevention of three line loss. To assess the consistency in treatment effect across lesion subtypes, we performed an analysis known as the Breslow-Day test. The analysis showed no evidence of interaction between neovascular AMD subtypes and Macugen treatment effect, demonstrating that the results for any single lesion subtype did not disproportionately contribute to the overall efficacy observed in the trials and that the treatment effect of Macugen is consistent across all subtypes. In December 2004, the FDA approved the use of the 0.3 mg dose of Macugen in the treatment of patients with all three

subtypes of subfoveal neovascular AMD. Moreover, the following chart depicts, for the combined patient populations of both trials, the mean change in visual acuity by subtype for patients treated with the 0.3 mg dose of Macugen and for patients in the control group. The mean change in visual acuity is expressed as the average number of letters lost by patients with each neovascular AMD subtype.



Secondary Endpoints and Other Clinical Observations. In addition to the primary endpoint data described above, we analyzed the results from the combined populations of patients from both trials treated with the 0.3 mg dose of Macugen to assess the degree, rate and sustainability of change in visual acuity compared to the combined control group populations.

To assess the degree of change in visual acuity, one of the secondary endpoints measured the proportion of patients whose visual acuity remained at baseline or improved over the 54-week trial period, and a second measured the proportion of patients whose visual acuity improved by 15 or more letters, or three or more lines, over the 54-week trial period. Although not prospectively specified in the trial protocols as secondary endpoints, we also assessed the proportion of patients who gained one or more lines of visual acuity over the 54-week trial period, the proportion of patients who gained two or more lines of visual acuity over the 54-week trial period and the proportion of patients who experienced severe loss of vision, defined as a loss of 30 or more letters, or six or more lines, of visual acuity over the 54-week trial period. The following table summarizes the combined results from both trials as to these secondary endpoints and additional analyses.

	Proportion of Patients		
	Macugen 0.3 mg	Control	p-value
Maintenance of or gain in vision:			
≥ 0 line vision gain	33%	23%	0.0032
Gain in vision:			
≥ 1 line vision gain	22%	12%	0.0043
≥ 2 line vision gain	11%	6%	0.0239
≥ 3 line vision gain	6%	2%	0.0401
Severe loss of vision:			
≥ 6 line vision loss	10%	22%	0.0001

All observations of the combined trial results summarized in the above table were statistically significant using the conventional p-value method, including the results from the two pre-specified secondary endpoints.

Additional secondary endpoints measured the rate and sustainability of Macugen's clinical effect. Specifically, these endpoints compared the mean change in visual acuity after six, 12 and 54 weeks between the combined populations from both trials receiving the 0.3 mg dose of Macugen and the combined populations from both trials in the control group. The following table summarizes the data for these secondary endpoints.

	Mean Change in Visual Acuity (Letters)		
Observation Period	Macugen 0.3 mg	Control	p-value
6 weeks	(1.5)	(4.0)	0.0069
12 weeks	(3.2)	(6.3)	0.0037
54 weeks	(8.0)	(15.0)	0.0000

These data suggest that the onset of clinical benefit for patients with neovascular AMD may be observed as early as six weeks after initial treatment. At 54 weeks, the combined population of patients from both trials receiving the 0.3 mg dose of Macugen on average continued to lose fewer letters of vision than patients in the combined control group. Furthermore, in the combined analysis, after 54 weeks, 62% more patients in the control group deteriorated to 20/200 visual acuity in the study eye than in the Macugen 0.3 mg dose group. A person is generally considered to be legally blind if their visual acuity is 20/200 or worse using both eyes with the benefit of corrective measures, such as eyeglasses.

Analysis of the data suggests that the overall efficacy is independent of lesion size and patient age. Specifically, statistical interaction tests indicate that efficacy is similar in small and large lesions as well as in younger and older patients. For these tests, small lesions were those of less than four disc areas, whereas large lesions were those of four or more disc areas, and younger patients were those less than 75 years of age, whereas older patients were those of 75 years of age or more.

Visudyne Use During the Trials. We did not design the trials to investigate the efficacy of Macugen treatment combined with photodynamic therapy using Visudyne. However, patients with a history of up to one prior administration of photodynamic therapy using Visudyne between 8 and 13 weeks before their first study visit were eligible for enrollment in our trials. Also, patients with predominantly classic subfoveal neovascular AMD at baseline who were eligible for Visudyne treatment could receive such treatment at baseline and during the studies at the discretion of the treating physician. Only 26% of all enrolled patients in the combined trials were eligible for Visudyne treatment at the beginning of the study. Of the 26% eligible, 65% actually received Visudyne treatment at any time. In addition, a small number of patients originally classified as minimally classic or occult converted to the predominantly classic subtype and received Visudyne. Overall, 75% of the patients in the trials did not receive any Visudyne treatment. Excluding those patients that received Visudyne treatment prior to study enrollment, investigators administered Visudyne treatment to approximately 50% more patients in the control group than in the Macugen 0.3 mg group. Overall, 24% more patients in the control group than in the Macugen 0.3 mg group received photodynamic therapy at any time, whether prior to, at or after baseline. The 0.3 mg dose of Macugen demonstrated a statistically significant, clinically relevant treatment benefit relative to control despite this higher rate of Visudyne usage in the control group. Therefore, we believe that the results of treatment with the 0.3 mg dose of Macugen are independent of Visudyne usage.

Safety. In the first year of the trials, Macugen was well-tolerated at all three doses. Our preliminary assessment of adverse event data indicates that there is no apparent increased risk of systemic adverse events to patients as a result of the use of Macugen. Few patients in either the treated or control groups discontinued their participation in the trials as a result of adverse events. Injection-related serious adverse events were low in number and included endophthalmitis, which is an infection of the eye, retinal detachment and physician-induced, or iatrogenic, traumatic cataract. During the first year of the trial, there were 12 cases of endophthalmitis reported, representing an incidence of 0.16% per injection or 1.3% per patient over the first year of treatment, six cases of retinal detachment reported, representing an incidence of 0.07% per injection or 0.6% per patient over the first year of treatment, and five cases of traumatic cataract, representing an incidence of 0.07% per injection or 0.6% per patient over the first year of treatment. Of the six cases of retinal detachment, two were exudative in nature and likely attributable to the underlying disease and four were due

to a tear or hole in the retina, known as rhegmatogenous, and may be attributable to the injection procedure. Only four of the patients who developed endophthalmitis experienced vision loss of 15 or more letters at week 54 compared to their baseline vision. Only one patient who developed endophthalmitis experienced severe vision loss of six or more lines, which represents approximately 0.1% of the patients treated with Macugen in the trials. The incidence of these injection-related adverse events is well within what we believe to be the tolerable limits for a drug that is administered by intravitreal injection. There was no evidence of drug-associated cataract or persistently elevated intraocular pressure or glaucoma in patients in the trials. Furthermore, the percentage of reported deaths was similar in the treated and control groups. We believe that the observed death rates and the serious adverse event profiles are consistent with those of the general population of patients with demographic characteristics similar to those of patients in the trials. Side effects from clinical and preclinical trials of systemic VEGF inhibitors have included hypertension, thromboembolic events, bleeding and proteinuria. None of these side effects was noted to have been associated with the use of Macugen, which is a non-systemic VEGF inhibitor, in our trials.

Second and Third Year of the Trials. Because of the role of the aging process in neovascular AMD, it was biologically plausible that continued neutralization of VEGF would be important beyond 54 weeks. Therefore, we followed up with patients beyond 54 weeks to determine, among other things, whether continued therapy with Macugen provides additional benefits and acceptable safety.

At week 54, patients originally assigned to Macugen injection were re-randomized on a 1:1 basis either to continue or discontinue therapy for a further eight injections over 48 weeks. Patients assigned to the control group in the first year of study were re-randomized either to receive sham injections for another year, to discontinue sham injections, or to receive one of the three tested doses of Macugen injection, 0.3 mg, 1.0 mg or 3.0 mg. Patients who were randomized to discontinue therapy were eligible to resume therapy if they had benefited from treatment in the first year and had lost at least two lines of vision after discontinuation. Approximately 90% of patients who received at least one treatment at baseline were re-randomized at week 54 of the study, and approximately 90% of such re-randomized patients were assessed at week 102 of the study. The mean number of treatments for patients re-randomized to continue therapy for a further 48 weeks was approximately 16 of a possible 17 total injections over two years.

In the combined analysis, from the start of the study to week 102, patients re-randomized to continue a second year of the 0.3 mg dose of Macugen lost an average of 9.4 letters of visual acuity compared to 17.0 letters of visual acuity for patients in the control group ($p<0.05$). In addition, 59% (78 out of 133) of patients re-randomized to continue a second year of 0.3 mg dose of Macugen lost less than 15 letters of visual acuity compared to 45% (48 out of 107) for patients in the control group ($p<0.05$). Thirty-five patients re-randomized to discontinue the 0.3 mg dose of Macugen lost more than 15 letters of visual acuity after week 54 compared to 21 patients re-randomized to continue a second year of such therapy ($p<0.05$). No systemic safety concerns and no new ocular safety issues emerged during the second year of the trial. The incidence of common ocular adverse events was similar to that in the first year of the trial. Most events reported in study eyes were mild-to-moderate in severity, transient, and attributed by investigators to the injection procedure rather than to the study drug.

During the second year of the trial, there was one case of traumatic cataract, representing an incidence of 0.02% per injection, seven cases of retinal detachment, representing an incidence of 0.17% per injection, and four cases of endophthalmitis, representing an incidence of 0.10% per injection. There was no evidence of cataract progression or persistent intraocular pressure elevation following multiple intravitreal injections. Macugen was well-tolerated systemically at all doses.

These Phase 2/3 clinical trials are ongoing to generate long-term safety data for up to five years so we may better characterize the long-term safety of Macugen.

Phase 1 and 2 Trials

We completed a Phase 1 and two Phase 2 clinical trials for the use of Macugen in the treatment of neovascular AMD prior to June 2001. The primary purpose of these trials was to test for product safety. In each of the three trials, Macugen was well tolerated, and there were no serious adverse events determined by

the clinical trial investigators as related to the drug. Although these trials were conducted on a relatively small number of patients and there were no randomized controls or long-term patient follow up, we observed encouraging effects of the drug on trial participants.

In the Phase 1 trial, 15 patients received escalating doses of Macugen one time via an intravitreal injection in the affected eye. The patients were distributed into five groups of three patients. Each group received a different dose of Macugen. In this trial, 80% of the patients showed stabilized or improved vision at the end of the three-month period following the injection. For purposes of this trial and our two Phase 2 trials described below, we defined stabilized vision as no loss of, or an increase in, letters of visual acuity on the ETDRS eye chart. Approximately 27% of the patients in this trial showed the ability to read 15 or more additional letters on the ETDRS eye chart at the end of the three-month period.

In the first open-label uncontrolled Phase 2 trial, 10 patients received Macugen via an intravitreal injection in the affected eye once a month for three months. Eight of the treated patients were tested at the end of the three-month period, with approximately 88% of the tested group showing stabilized or improved vision and 25% showing the ability to read 15 or more additional letters on the ETDRS eye chart at the end of the three-month period.

In the second open-label uncontrolled Phase 2 trial, 11 patients received Macugen via intravitreal injection in the affected eye once a month for three months. This trial consisted solely of patients with the predominantly classic form of subfoveal neovascular AMD who also received photodynamic therapy with Visudyne shortly before their first injection of Macugen. Ten of the treated patients were tested at the end of the three-month period, with 90% of the tested group showing stabilized or improved vision and 60% showing the ability to read an additional 15 or more letters on the ETDRS eye chart, which is three lines on the Snellen chart, at the end of the three-month period.

Phase 4 Trials

We are planning to conduct a Phase 4 combination trial with Macugen and Visudyne versus Macugen alone, to determine if patients with the predominantly classic form of macular degeneration benefit from combination therapy. The study, which is anticipated to start in the second quarter of 2005, will be conducted in both United States and international centers.

During the first quarter of 2006, we are planning to launch a Phase 4 clinical trial which will satisfy our clinical post-approval commitments to the FDA. This clinical trial will explore the safety and efficacy of the FDA approved 0.3 mg dose of Macugen versus two additional lower doses of Macugen in patients with subfoveal, neovascular AMD. Endpoints include mean changes in vision and the effects on the neuro-sensory retina and corneal endothelium.

Phase 2 Pharmacokinetic Study

In January 2003, we began a Phase 2 clinical trial designed to obtain additional pharmacokinetic data from the use of Macugen in the treatment of neovascular AMD. The 147 patients enrolled in this trial each receive one year of treatment. Treatment occurs every six weeks. Entry criteria for this trial were similar to those for our Phase 2/3 pivotal clinical trials. We conduct extensive blood sampling for pharmacokinetic data for each patient on two occasions during the trial. Safety endpoints are secondary endpoints of the trial.

Clinical Trials for the Treatment of Diabetic Macular Edema

Phase 2/3 Trial

We and Pfizer are currently in discussions with regulatory authorities regarding the design of a Phase 2/3 clinical trial program for the use of Macugen in the treatment of DME. We currently expect to begin dosing patients in this Phase 2/3 clinical trial for this indication in the second half of 2005.

Phase 2 Trials

We have completed one Phase 1/2 clinical trial for the use of Macugen in the treatment of DME. In this trial, clinical centers enrolled 10 patients with DME. Patients were administered an intravitreal injection in the affected eye once a month for three months. As in the neovascular AMD Phase 1 and 2 studies, the therapy was well tolerated, and there were no serious adverse events determined by the clinical trial investigators as related to the drug or its administration.

In February 2005, we completed a second Phase 2 clinical trial for the use of Macugen in the treatment of DME. The 169 patients enrolled in this study were required to have been eligible for laser therapy for DME. In this randomized, double-masked placebo controlled trial, patients received 0.3 mg, 1 mg, 3 mg doses of Macugen via intravitreal injection or sham control injections every six weeks for at least 12 weeks and then up to 30 weeks at the discretion of the investigators.

We announced the results from the active treatment phase of this Phase 2 clinical trial and the following table summarizes these results up to 36 weeks.

	Proportion of Patients		
	Macugen 0.3 mg	Control	p-value
Maintenance of or gain in vision:			
≥ 0 line vision gain	73%	51%	0.02
Gain in vision:			
≥ 1 line vision gain	59%	34%	0.01
≥ 2 line vision gain	34%	10%	0.003
≥ 3 line vision gain	18%	7%	—

These data from our Phase 2 clinical trial in DME were statistically significant using the Hochberg method for the 0.3 mg dose of Macugen compared to control with respect to 0 or greater, 1 or greater and 2 or greater line gainers at 36 weeks. The preliminary data also showed a trend for Macugen treated eyes to be more likely to gain 3 or more lines than controls. The lowest efficacious dose for this trial, 0.3 mg, was the same as that for our Phase 2/3 pivotal clinical trial for the use of Macugen in the treatment of neovascular AMD.

Optical coherence tomography, an imaging technique, which may anatomically quantify retinal thickness or edema, showed a 300% relative reduction trend in retinal thickness for the 0.3 mg dose of Macugen compared to controls (50.79 microns compared to 12.68 microns). In the geometric center of the macula, that region directly responsible for high acuity vision, the odds of a decrease in retinal thickness of 75 μm or more is 4 times larger for 0.3 mg dose of Macugen group compared to controls (p=0.0078).

A preliminary look at the draft safety data suggests that Macugen is well-tolerated in patients with DME. Further detailed analyses of both the safety and efficacy data up to one year after the last dose of study drug are ongoing.

Clinical Trials for the Treatment of Retinal Vein Occlusion

In the second quarter of 2004, we commenced a Phase 2 clinical trial designed to test the efficacy and safety of Macugen for the treatment of RVO, a condition that is characterized by high VEGF levels, abnormal blood vessel growth and blood vessel leakage. RVO occurs when the circulation of a retinal vein becomes obstructed, causing blood vessel bleeding and leakage in the retina. Laser therapy is sometimes used to treat

this condition, but with limited efficacy. We currently have enrolled 35 patients and plan to enroll approximately 90 patients, all of whom we plan to treat for between 12 and 30 weeks. We plan to continue to expand the study to include patients from additional European and Australian sites in the second quarter of 2005. The endpoints will include changes in visual acuity and retinal thickness measured by optical coherence tomography and angiographic changes at week 30 and one year.

Collaboration with Pfizer

Macugen

In December 2002, we entered into several concurrent agreements with Pfizer to jointly develop and commercialize Macugen for the prevention and treatment of diseases of the eye and related conditions. Under the terms of our collaboration agreements with Pfizer:

- Pfizer has funded, and is obligated to continue to fund, a majority of the ongoing development costs incurred pursuant to an agreed upon development plan covering the development of Macugen for AMD, DME, RVO and other agreed upon ophthalmic indications;
- In the United States, we are co-promoting Macugen with Pfizer through our own and Pfizer's sales forces and we and Pfizer will share in profits and losses from the sale of Macugen, with our having the right to book all United States product sales; and
- Outside the United States, Pfizer will market the product under an exclusive license, for which we will receive royalty payments based on net sales.

Pfizer has made the following payments and investments to date under our collaboration:

- In February 2003, upon effectiveness of the collaboration arrangements, Pfizer paid us $100 million, consisting of a $75 million initial license fee and a $25 million equity investment;
- In February 2004, Pfizer purchased an additional $10 million of our common stock at the closing of our initial public offering;
- In September 2004, Pfizer paid us $10 million after the acceptance for review by the FDA of our NDA for the use of Macugen in the treatment of neovascular AMD;
- In October 2004, Pfizer paid us $5.5 million after the European Medicines Agency's acceptance of the filing of Pfizer's marketing authorization application for Macugen for use in the treatment of neovascular AMD;
- In January 2005, Pfizer paid us a $90 million license fee after the approval in December 2004 by the FDA of Macugen for the treatment of neovascular AMD; and
- In February 2005, Pfizer purchased 344,000 shares of our common stock at a purchase price of approximately $43.60 per share for total proceeds of $15 million after the approval by the FDA of Macugen for the treatment of neovascular AMD.

In the future, Pfizer may be obligated to make additional payments under the following circumstances:

- Up to $90 million in additional payments based on the achievement of additional worldwide regulatory submissions and approvals; and
- Up to $450 million in payments based upon attainment of agreed upon sales levels of Macugen.

Under the agreements, the parties' sharing of profits and losses from the commercialization of Macugen in the United States extends until the later of 15 years after commercial launch in the United States and the expiration of the United States patent rights licensed to Pfizer. The payment of royalties to us by Pfizer based on net sales of Macugen outside the United States extends, on a country-by-country basis, until the later of 15 years after commercial launch and the expiration of the patent rights licensed to Pfizer in each particular country. The royalty rate on net sales of Macugen outside the United States is reduced on a country-by-country basis to the extent that the patent rights in a particular country expire or a generic form of Macugen is

marketed in that country. We commercially launched Macugen in January 2005. The United States patent rights licensed by us to Pfizer expire between 2010 and 2017. The corresponding foreign rights include patents that expire between 2011 and 2017 and patent applications which, if issued as patents, are expected to expire between 2011 and 2020. Pfizer may terminate the collaboration relationship without cause upon six to twelve months' prior notice, depending on when such notice is given. Either party may terminate the collaboration relationship based upon material uncured breaches by the other party. In addition, we may terminate the collaboration relationship if, during specified periods, net sales of Macugen do not reach specified levels. If we elect to terminate the collaboration in this situation, we would be required to pay royalties to Pfizer based on net sales of Macugen following such termination.

The collaboration is governed by a joint operating committee, consisting of an equal number of representatives of us and Pfizer. There are also subcommittees with equal representation from both parties that have responsibility over development and regulatory, manufacturing and commercialization matters. In the case of unresolved disagreement, ultimate decision-making authority is vested in us as to some matters and in Pfizer as to other matters. A third category of decisions requires the approval of both us and Pfizer. Outside the United States, ultimate decision-making authority as to most matters is vested in Pfizer.

Xalatan

In connection with the Macugen collaboration, we entered into an agreement with Pfizer under which our sales force is entitled to participate in selling activities, or detailing, with respect to Pfizer's Xalatan glaucoma product on a nonexclusive basis in the United States. Xalatan is a once-a-day prescription eye drop marketed by Pfizer as a primary, or first line, therapy for glaucoma, an eye disease that is associated with the degeneration of the retinal cells responsible for transmitting images from the eye to the brain.

Under this agreement, Pfizer is obligated to pay us a per detail fee for our details to general ophthalmologists and a percentage of incremental net revenues that are above a baseline threshold for our details to retinal specialists. The agreement automatically terminates upon a termination of the Macugen collaboration or upon Pfizer's sale, assignment, exclusive license or other disposition of the Xalatan product. In addition, we may terminate the agreement upon four months' prior notice. Either party may terminate the agreement based upon material uncured breaches by the other party.

We view the Xalatan agreement as primarily a strategic arrangement and anticipate only a modest economic impact. We are currently focusing our sales force entirely on Macugen and are not currently detailing Xalatan. We and Pfizer will continue to assess the benefits of having our sales force initiate detailing of Xalatan, but do not have any current plans to do so.

Pipeline Initiatives

In order to expand our pipeline of products to treat diseases of the eye with unmet medical need, we are actively pursuing a strategy to develop new drugs internally and to license or otherwise acquire rights to potential new drugs from third parties. We are also seeking to develop internally and acquire rights to alternative mechanisms for delivering ophthalmic drugs to the back of the eye. For example, since April 2004, we have had a research and collaboration agreement with Archemix that allows us to develop the current pipeline of Archemix in the field of ophthalmology. This agreement also provides us with the ability to have Archemix select new aptamers against our targets included in the research program for further development by us in ophthalmology.

We conduct our internal research and development activities at our Eyetech Research Center located in Lexington, Massachusetts. We had 65 full-time employees at this facility, including a total of 23 employees who hold M.D. and/or Ph.D. degrees, as of March 1, 2005. We are conducting research into the causes of AMD and diabetic retinopathy as well as novel methods of drug delivery to the back of the eye. We also are investigating the use of Macugen for non-ophthalmic indications. We have developed proprietary models that accelerate the study of disease processes and the identification and validation of attractive molecular targets for ophthalmic drug development. We have also developed tools for studying the basic disease processes involved in the degeneration of retinal cells associated with glaucoma.

Our current pipeline initiatives include the following:

Additional Ophthalmic Indications for Macugen

In addition to neovascular AMD, DME and RVO, there are a number of ophthalmic conditions with medical need for which the VEGF inhibition of Macugen may prove beneficial. We are conducting preclinical animal tests to assess the potential therapeutic benefit and/or drug delivery applications of Macugen for the treatment of the following indications:

- "High risk" dry AMD, in which the patient is at risk of developing neovascular AMD more rapidly than other dry AMD patients. It is possible to identify this form of dry AMD through a routine eye examination. We believe that these high risk patients may benefit from treatment with Macugen to control the progression of high risk dry AMD to neovascular AMD.
- Proliferative diabetic retinopathy, the most severe stage of diabetic retinopathy. The disease is characterized by angiogenesis and blood vessel leakage. The new vessels frequently bleed and damage the retina. Although laser therapy is effective at lowering the rate of blindness associated with the disease, the destruction of the retina resulting from the treatment leads to adverse side effects, including night blindness and visual field loss.
- Uveitis, an inflammatory condition of the eye that often leads to macular edema. The swelling is largely a function of increased blood vessel leakage. Steroids are effective in some cases as a treatment for this condition, although their use is often complicated by the formation of cataracts and glaucoma.
- Cystoid macular edema following cataract surgery, a condition that results from the inflammation caused by surgery. Steroid treatment is effective in some patients, but carries the risk of cataracts and glaucoma.
- Myopic macular degeneration, a condition in which a patient with a high degree of nearsightedness develops choroidal neovascularization. The blood vessel growth and leakage in this condition closely mirrors that seen in neovascular AMD.
- Inflammatory macular degeneration, a condition in which a patient with inflammation in the macular area from infections or other causes develops choroidal neovascularization. The blood vessel growth and leakage in this condition is similar to that seen in neovascular AMD.
- Iris neovascularization, a serious complication of diabetic retinopathy or RVO involving new blood vessel growth on the surface of the colored part of the eye, or iris. This process leads to an intractable type of glaucoma that often leads to blindness. Animal testing has revealed that this process involves VEGF.

Alternate Delivery Technologies

We believe that technologies for the long-term administration of drugs to the back of the eye that are more convenient for physicians and patients than existing methods may expand the potential markets for Macugen and other ophthalmic therapies. We are working to develop alternative, more convenient long-term drug delivery technologies. In particular, we have a number of alternative delivery methods in preclinical tests. The approaches that we are exploring include alternative drug formulations that may permit less frequent administration of Macugen.

Other Ophthalmic Drugs

Through our research activities, we are seeking to develop other novel drugs to treat other ophthalmic diseases, including drugs that may enhance the efficacy of Macugen. We have identified distinct molecular targets in addition to VEGF that we believe are attractive sites for pharmaceutical intervention to treat ophthalmic blood vessel disease. One of these targets is involved in the formation of new blood vessels through a process that is independent of the activity of VEGF. A second target affects blood borne cells involved in the formation of new vessels and abnormal vessel leakage. This second target also plays a role in the development

and progression of diabetic retinopathy. In animal studies, the second target was operative at all stages of diabetic retinopathy and the inhibition of this target both prevented and reversed diabetic retinopathy. Human correlative data also support the role of this target in human diabetic retinopathy.

Included in our exclusive agreement with Archemix to collaborate on the research and development of aptamers for ophthalmic indications, are optimized aptamers in the existing Archemix pipeline portfolio as well as new aptamers discovered through the use of Archemix's proprietary SELEX process in the research program. Archemix also has the option to propose future aptamers discovered outside of this collaboration for inclusion in the program for the treatment of ophthalmic indications. Through the collaboration, we have access to a broad proprietary research platform for generating candidates for generating future optimized lead compounds for development in ophthalmology. We have the responsibility for all clinical development activities, and have the right to commercialize all program aptamers for ophthalmologic indications. Archemix received an initial payment from us and will also receive payments for achievement of certain research and development milestones, and royalties on net sales of all products resulting from the collaboration. We also provide support for efforts carried out by Archemix in support of the collaboration.

We are directing our research at developing drugs against these and other targets that can be used either alone or in combination with Macugen therapy for the treatment of eye diseases. We are also seeking opportunities to license or develop drug candidates that address these and other targets.

Additional Non-Ophthalmic Indications for Macugen

VEGF appears to play a pivotal role in several non-ophthalmic diseases, including cancer. We are using our preclinical expertise to research the potential application of Macugen outside of ophthalmic indications. Because these diseases are outside of our core expertise in ophthalmology and are not part of our collaboration with Pfizer, we expect to pursue collaboration or outlicensing opportunities if our research suggests that Macugen is a promising therapy.

Solid tumors and their metastases rely on new blood vessel growth for their survival. VEGF has been extensively validated in numerous preclinical trials as a drug target for the treatment of some types of cancers. In addition, Genentech Inc. recently received approval of its drug candidate Avastin™, validating VEGF as a drug target for renal cancer and colon cancer. We believe that we may be able to formulate novel locally administered, sustained release versions of Macugen for use in the treatment of some types of solid tumors. We expect that these formulations would be used at the time of cancer surgery to provide therapy directly at the site of the disease. We believe that these Macugen formulations might possess advantages over intravenously administered drugs. For example, a locally administered formulation of Macugen might be able to access some types of brain tumors that are not accessible to anti-VEGF drugs administered intravenously.

Sales and Marketing

The ophthalmic medical community in the United States is relatively small. We estimate that in the United States there are approximately 2,000 specialists that treat retinal disease, including 1,400 members of retinal subspecialty societies, who perform most of the medical procedures involving back of the eye diseases. Because of the small size of our target provider audience in the United States, we believe that we can best serve this market through our dedicated specialty sales force. Our sales team consists of 60 people with significant experience gained at large pharmaceutical and biotechnology companies, covering sales, sales management, reimbursement issues and education of doctors. Under our United States co-promotion arrangement with Pfizer for Macugen, our sales force has primary responsibility for promoting and detailing Macugen to retinal specialists, and Pfizer will also target retinal specialists in partnership with us, and has primary responsibility for promoting Macugen to general ophthalmologists. Pfizer's ophthalmics sales force consists of approximately 160 representatives.

Prior to our launch of Macugen in January 2005, we had not marketed or sold any products as a company. To achieve commercial success for Macugen, our sales and marketing organization must work with our partner, Pfizer, to effectively integrate our sales and marketing infrastructures and implement our sales and marketing efforts. If our sales and marketing efforts are not successful our business will materially suffer.

Outside the United States, we currently plan to market and sell our products that receive regulatory approval through established industry participants. However, we may determine to establish our own sales and marketing organization in key markets, including the European Union. We have granted Pfizer exclusive commercialization rights with respect to Macugen outside the United States.

Distribution and Pricing

We distribute Macugen in the United States primarily through national distributors that specialize in pharmaceutical product distribution to specialty markets. In January 2005, we announced the distribution of Macugen to retinal specialists through three distributors: McKesson Specialty, Priority Healthcare and Besse Medical. Under this arrangement, we ship Macugen to our distributors and title and risk of loss pass upon shipment to the distributors. These distributors sell Macugen to physicians, physician group practices, hospitals, federal government buying groups and clinics. The list price to distributors for Macugen is currently $995 per unit.

Manufacturing

We have a limited number of personnel with experience in, and we do not own or lease operating facilities for, manufacturing Macugen. In November 2004, we acquired a manufacturing facility in Boulder, Colorado that we plan to develop for use as a second source of supply for the active pharmaceutical ingredient in Macugen, but that facility is not currently operational for such purpose. Accordingly, unless or until we develop or acquire sufficient manufacturing capabilities, we will depend on third parties to manufacture Macugen and any future products that we may develop or acquire.

The manufacturing process of the active pharmaceutical ingredient of Macugen consists of chemical synthesis of the oligonucleotide, purification, PEGylation, further purification and finally freeze drying to form a powder. Each of these steps involves a relatively common chemical engineering process. The chemical synthesis uses conventional synthetic techniques for this type of molecule. The components of the active pharmaceutical ingredient are generally available from a number of suppliers. However, we rely on a single source of supply for PEGylation reagent.

For our clinical trials of Macugen, we engaged a third party manufacturer, Raylo Chemicals Inc., an independently operating subsidiary of Degussa AG, or Degussa, to produce the active pharmaceutical ingredient used in Macugen. In November 2003, we entered into an agreement with the subsidiary of Degussa for the commercial manufacture and supply of the active pharmaceutical ingredient. Degussa manufactured active pharmaceutical ingredient for our clinical supplies and now manufactures the active pharmaceutical ingredient use in our commercial product.

Under the terms of our agreement with Degussa, we are obligated to purchase all of our requirements for the active pharmaceutical ingredient from Degussa through 2005 and to purchase minimum specified percentages of our requirements for the active pharmaceutical ingredient thereafter. We are required to provide Degussa with binding forecasts of our orders for each calendar quarter at least two months prior to the commencement of the calendar quarter. Degussa is obligated to satisfy our orders in a timely manner up to 100% of our binding forecasts and to use its best efforts to satisfy our orders in excess of these binding forecasts. The purchase price for the active pharmaceutical ingredient is calculated on a cost-based formula that adjusts over time depending on a variety of factors. We are also required to reimburse Degussa for royalties payable to a third party for intellectual property related to the manufacturing process. The initial term of the agreement is five years. We have the right to extend the agreement, at our option, for up to an additional six years. We have the right to terminate the agreement if Degussa fails to supply at price levels that are as low as those available to us from an alternative supplier after December 31, 2005, if we abandon our efforts to commercialize Macugen, if Degussa is not able to meet specified legal and regulatory requirements or if a change in control of Degussa occurs. In addition, either party may terminate the agreement if the other party materially breaches the agreement and fails to cure the breach or in the event of the bankruptcy, liquidation or insolvency of the other party.

For our clinical supply of Macugen, we also engaged Gilead Sciences, Inc. as a separate fill and finish manufacturer to formulate the active pharmaceutical ingredient from a solid into a solution and to fill the solution into syringes. In December 2003, we entered into an agreement with Gilead to provide fill and finish services for the commercial supply of Macugen. Under the terms of the agreement, we are obligated to purchase all of our requirements for these fill and finish services from Gilead through the first anniversary of the January 2005 commercial launch of Macugen in the United States and to purchase minimum specified percentages of our requirements through the third anniversary of the January 2005 commercial launch of Macugen in the United States. The purchase price for the fill and finish services is based on fixed batch and per-unit charges that vary depending on annual order volumes and additional costs that depend on costs of materials procured from third parties and Gilead's costs of providing specified ancillary services not covered by the fixed batch and per-unit charges. The term of the agreement runs through the third anniversary of the January 2005 commercial launch of Macugen in the United States. We have the right to terminate the agreement if we abandon our efforts to develop and commercialize Macugen, if Gilead fails to achieve specified order fulfillment requirements or is unable to manufacture in accordance with regulatory requirements, if Gilead acquires, is acquired by or becomes an affiliate of, a company that is a manufacturer, supplier or distributor of a product competitive with Macugen or in the event of the bankruptcy or insolvency of, or appointment of a receiver for, Gilead. In addition, either party may terminate the agreement if the other party materially breaches the agreement and fails to cure the breach or if either party is prevented by a force majeure event from performing its obligations under the agreement for more than three months.

In order to sustain Macugen supply at the quantities we believe will be necessary to meet anticipated future market demand, we and our contract manufacturer will need to increase the manufacturing capacity for the active pharmaceutical ingredient for Macugen. We believe we have sufficient capacity to supply the active pharmaceutical ingredient and to manufacture Macugen to meet anticipated demand through the first quarter of 2007. We initially intend to increase manufacturing capacity for the active pharmaceutical ingredient by duplicating a portion of our manufacturing lines at the Degussa manufacturing facility. We also intend to invest in appropriate infrastructure at the manufacturing facility that we acquired in Boulder, Colorado in late 2004, to prepare the facility to become a second source for commercial scale production of the active pharmaceutical ingredient for Macugen. We will also continue to explore other alternatives for increasing manufacturing capacity. We are also investing to increase the capacity for finished product manufacturing at Gilead and to improve the related packaging operation. If we are unable to increase our manufacturing capacity or are delayed in doing so, we may not be able to produce Macugen in a sufficient quantity to meet future requirements to sustain supply of the product to meet anticipated future demand. In addition, the cost of increasing manufacturing capacity may be expensive. Our revenues and gross margins could be adversely affected by any inability to meet demand and the increased cost in increasing manufacturing capacity.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party because of factors beyond our control; and
- the possibility of termination or non-renewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us.

License Agreements

We are parties to two license agreements that we believe are material to our business.

Gilead Sciences

In March 2000, we entered into an agreement with Gilead and its wholly-owned subsidiary NeXstar Pharmaceuticals, Inc. for an exclusive worldwide license, under the patents and know-how related to Macugen controlled by Gilead and its affiliates, to develop, manufacture and commercialize products containing

Macugen. This license extends to all therapeutic indications. Subject to a right of first negotiation in favor of Gilead as to a limited set of indications, we have the right to grant sublicenses under this license.

In exchange for the rights licensed from Gilead, we paid Gilead an up-front license fee of $7.0 million and issued Gilead a warrant, which was subsequently exercised in full on a cashless basis during the quarter ended March 31, 2004, resulting in the issuance to Gilead of 680,509 shares of our common stock. We also agreed to make payments to Gilead aggregating up to $25 million based on achieving specified development and commercial launch milestones, $15.0 million of which has been paid to date, including $5.0 million in July 2004, $3.0 million in October 2004 and $7.0 million in February 2005, and to pay royalties to Gilead based on net sales of Macugen by us or our affiliates or sublicensees. Our royalty obligation extends on a country-by-country basis until the later of 10 years after first commercial sale of Macugen, which occurred in January 2005, or the expiration of the last-to-expire patent licensed from Gilead in each particular country. The United States patent rights relating to Macugen licensed to us by Gilead expire between 2010 and 2017. The corresponding foreign rights include patents that expire between 2011 and 2017 and patent applications which, if issued as patents, are expected to expire between 2011 and 2019. Upon the expiration of the last-to-expire royalty term, the agreement expires and, at our option, our license from Gilead either (1) survives and remains exclusive, in which case we would be obligated to continue paying Gilead a reduced royalty on product sales or (2) survives and converts to nonexclusive, in which case would not have any further royalty obligation to Gilead. The agreement obligates us to use commercially reasonable efforts to develop, obtain regulatory approvals for and commercialize Macugen. Each party has the right to terminate the agreement if the other party materially breaches the agreement.

Nektar Therapeutics

In February 2002, we entered into a license, manufacturing and supply agreement with Nektar Therapeutics, formerly Shearwater Corporation, relating to the PEGylation of Macugen. Pursuant to that agreement, Nektar supplies us with the reagent that we link to the aptamer to create the active pharmaceutical ingredient in Macugen. Under the terms of the agreement, Nektar granted us various exclusive and nonexclusive worldwide licenses, with the right to grant sublicenses, under patents and know-how related to the reagent controlled by Nektar, to develop, manufacture and commercialize Macugen.

In exchange for these rights, we paid Nektar an up-front license fee of $1.5 million and, in January 2005, we paid an additional $3.0 million in connection with the FDA's marketing approval of Macugen. We also agreed to pay Nektar royalties based on net sales of Macugen by us or our affiliates or sublicensees. The $3.0 million payment made in January 2005 will be fully credited against a portion of the royalty payments that we may be required to make to Nektar. We also agreed to purchase the PEGylation reagent for Macugen exclusively from Nektar, subject to Nektar meeting its supply obligations.

Unless we and Nektar agree to extend the term, the agreement expires upon the expiration of the last-to-expire patent licensed by us from Nektar. The United States patent rights licensed to us by Nektar expire between 2013 and 2016. The corresponding foreign rights include a patent that expires in 2015 and patent applications which, if issued as patents, are expected to expire between 2015 and 2020. The agreement imposes development and commercialization diligence requirements on us. Each party has the right to terminate the agreement if the other party materially breaches the agreement and upon the occurrence of specified bankruptcy or insolvency events as to the other party.

Patents and Proprietary Rights

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing United States and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

We own or license a total of 27 United States patents and 29 United States patent applications as well as numerous foreign counterparts to many of these patents and patent applications. Our patent portfolio includes patents and patent applications with claims covering the composition of matter and methods of manufacturing and use of Macugen, as well as the composition of matter and method of manufacturing of both modified and unmodified aptamers in general and modified and unmodified VEGF aptamers in particular. In addition, we have patent applications covering various aspects of ophthalmic drug delivery.

We license patent rights from other patent owners from time to time, both on an exclusive basis and on a nonexclusive basis. Examples of such patent licenses include the patent rights that we have licensed from Gilead and Nektar and a nonexclusive, royalty-bearing patent license that we entered into with Isis Pharmaceuticals, Inc. in December 2001, which grants us rights under patents owned or controlled by Isis to make, have made, use and sell the Macugen compound worldwide. In addition to the obligation to pay royalties to Isis, we paid an initial license fee of $2.0 million and regulatory milestones of $4.0 million, $1.0 million of which was paid in July 2004 and $3.0 million of which was paid in January 2005. We also agreed to make payments aggregating up to $2.75 million based on achieving specified regulatory milestones with respect to the use of Macugen for other therapeutic indications.

United States patents generally have a term of 20 years from the date of filing. The patent rights relating to Macugen owned and licensed to us by Gilead consist of 15 United States patents that expire between 2010 and 2017 and counterpart filings to these patents in a number of other jurisdictions, including patents issued in several jurisdictions and patent applications pending in a number of other jurisdictions, including Europe and Japan. The patents licensed to us by Nektar consist of 10 United States patents that expire between 2013 and 2016 and foreign counterpart filings to these patents in a number of jurisdictions. The patents licensed to us by Isis consist of two United States patents that expire in 2010 and 2014 and foreign counterpart filings to these patents in a number of jurisdictions.

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 claims and enforcing those claims once 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. Our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated or circumvented, which could limit our ability to stop competitors from marketing related products or the length of term of patent protection that we may have for our products. In addition, the rights granted under any issued patents may not provide us with proprietary protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of the patent.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and other contractors. 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 employees, consultants or contractors 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.

Competition

The development and commercialization of new drugs and drug delivery technologies is highly competitive. We will face competition with respect to Macugen and any products we may develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide.

Macugen competes against the currently approved therapies for the treatment of neovascular AMD described above under the caption "— Eye Disease — Limitations of Currently Available Therapies for Neovascular AMD." If we receive marketing approval for the use of Macugen in the treatment of DME, Macugen would compete against currently approved treatments for DME described above under the caption "— Eye Disease — Limitations of Currently Available Therapies for DME." There are also a number of companies working to develop new drugs and other therapies to treat neovascular AMD and DME. We believe that the following product candidates are in Phase 2 or Phase 3 clinical trials:

- Genentech, Inc. and Novartis are collaborating to develop a humanized monoclonal antibody fragment, administered by intravitreal injection, that targets VEGF for the treatment of neovascular AMD. This product candidate has been viewed as particularly competitive with Macugen because of the similarity of its mechanism of action. Preliminary results of Phase 3 clinical trials for this product candidate will likely be released this year.
- Alcon, Inc. is developing anecortave acetate, an angiostatic steroid-based compound for the treatment and prevention of neovascular AMD that features a less invasive injectable delivery that requires less frequent administration (every six months). This drug candidate is injected behind the eye using a customized injector inserted around the eye. In August 2004, Alcon announced that it did not meet it primary endpoint in its pivotal Phase 3 clinical trial of this compound. Alcon has received priority review status from the FDA under its fast track, Pilot 1 program, has announced that it expects an FDA decision on its NDA in May 2005 and has submitted its European marketing authorization application for a drug suspension to be approved as a treatment for patients with subfoveal choroidal neovascularization due to AMD. Further, Alcon is enrolling patients in two Phase 3 clinical trials, one in South America and one in Europe, comparing the safety and efficacy of its compound against placebo in patients with all subtypes of neovascular AMD. Alcon also has initiated a five-year Phase 3 risk reduction trial for the prevention of neovascular AMD.
- Allergan, Inc., which recently acquired Oculex Pharmaceuticals, is developing a bioerodable steroid implant for the treatment of persistent macular edema.
- Eli Lilly & Co. is developing an orally administered inhibitor of an enzyme named PKC beta for the treatment of diabetic retinopathy.
- Bausch & Lomb Incorporated and Control Delivery Systems, Inc. are developing a surgically placed non-erodable intraocular implant for the delivery of steroids to treat DME and swelling resulting from other causes.
- Regeneron Pharmaceuticals, Inc. is developing a receptor fusion protein in ophthalmology that contains portions of the extracellular domains of two different VEGF receptors and announced the start of a Phase 1 clinical trial in AMD in March 2004.
- Miravant Medical Technologies is developing a photodynamic therapy that is similar to Visudyne for the treatment of neovascular AMD.
- Genaera Corporation is developing a small molecule derived from the Dogfish shark and is conducting three Phase 2 clinical trials and has announced plans to start a Phase 3 trial in the first half of 2005 for the treatment of AMD.
- Sirna Therapeutics, Inc. is developing a chemically modified short interfering RNA (siRNA) and announced the start of a Phase 1 clinical trial in neovascular AMD in November 2004.
- Acuity Pharmaceuticals, Inc. is developing a small molecule interfering RNA VEGF inhibitor for the treatment of neovascular AMD that is in early clinical trials.
- Pfizer is developing a small molecule VEGF inhibitor for the treatment of neovascular AMD that is in early clinical trials.

In addition, there are a number of other companies that are developing anti-VEGF technologies. Some of these companies may seek to apply their technologies to AMD, DME and other ophthalmic indications.

The key competitive factors affecting the success of Macugen are likely to be its:

- efficacy,
- safety profile,
- price relative to other treatments,
- reimbursement status, and
- method of administration.

The favorable efficacy and safety profile of Macugen have been demonstrated by the results from our clinical trials to date which are described above under the caption "— Clinical Trial for the Treatment of Neovascular AMD," and confirmed by the marketing approval of Macugen by the FDA for use in all subtypes of neovascular AMD, a broader product label than other FDA-approved products for neovascular AMD in the United States market. The efficacy and safety profile of Macugen will continue to develop as we continue our clinical trials and experience with the product is gained in the commercial marketplace. Macugen is currently priced at a premium to other approved treatments for neovascular AMD that we believe fairly reflects the product's efficacy and safety profile. We have established and implemented a reimbursement strategy designed to increase the competitive status of Macugen in the neovascular AMD market through competitive reimbursement economics for the medical community and access to helpful resources to assist the medical community and patients in gaining reimbursement. Our reimbursement strategy includes employing reimbursement experts and other resources that we have made available to our target medical community and patients to assist them in gaining reimbursement for Macugen and a pre-determined code for reimbursement of the intravitreal injection procedure in the Medicare system. The method of administration of Macugen, intravitreal injection, is commonly used to administer ophthalmic drugs and generally accepted by patients facing the prospect of blindness and other serious back of the eye complications such as DME. However, a therapy that offers a less invasive method of administration may have a competitive advantage over one administered by intravitreal injection.

Competitive therapies may result in product pricing pressure even if Macugen is otherwise viewed as a preferable therapy. Future competitive products may have superior efficacy, improved safety and convenience or reduced frequency of administration compared to Macugen. Because Macugen is currently our only FDA-approved product, any product that arises with superior efficacy, improved safety and convenience or reduced frequency of administration compared to Macugen may have a material adverse affect on our business. Even the expectation that a competitive product may gain marketing approval to compete with Macugen may have a negative effect on the trading price of our common stock.

The licensing and acquisition of pharmaceutical products, which is part of our strategy, is a highly competitive area. A number of more established companies also are pursuing strategies to license or acquire products. These established companies may have a competitive advantage over us due to their size, cash flow and institutional experience.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, promotion, advertising, distribution, marketing and export and import of pharmaceutical products such as those we are developing.

United States Government Regulation

In the United States, the FDA regulates drugs and biologics under the Federal Food, Drug, and Cosmetic Act, and, in the case of biologics, also under the Public Health Service Act, and implementing regulations. If we fail to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or

revocation, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency enforcement action could have a material adverse effect on us.

The steps required before a drug or biologic may be marketed in the United States include:

- preclinical laboratory tests, animal studies and formulation studies under FDA's good laboratory practices regulations;
- submission to the FDA of an Investigational New Drug application, or IND, for human clinical testing, which must become effective before human clinical trials may begin;
- adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each indication;
- submission to the FDA of a New Drug Application, or NDA, or Biologics License Application, or BLA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practice, or cGMP; and
- FDA review and approval of the NDA or BLA.

Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. The IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. Submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Each trial must be reviewed and approved by an independent Institutional Review Board before it can begin. Phase 1 trials usually involve the initial introduction of the investigational drug into humans to evaluate the product's safety, dosage tolerance and pharmacodynamics and, if possible, to gain an early indication of its effectiveness.

Phase 2 trials usually involve controlled trials in a limited patient population to:

- evaluate dosage tolerance and appropriate dosage;
- identify possible adverse effects and safety risks; and
- evaluate preliminarily the efficacy of the drug for specific indications.

Phase 3 trials usually further evaluate clinical efficacy and test further for safety in an expanded patient population. Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. Furthermore, the FDA or we may suspend or terminate clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacture and composition of the product, are submitted to the FDA in the form of an NDA or BLA requesting approval to market the product for one or more indications. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use. The FDA reviews a BLA to determine, among

other things, whether the product is safe, pure and potent and the facility in which it is manufactured, processed, packed or held meets standards designed to assure the product's continued safety, purity and potency.

As part of the drug approval process, we must conduct a comprehensive assessment of the carcinogenic potential of our product candidates. This often requires the completion of several in vitro tests and tests in laboratory animals designed to detect compounds that may induce cancer directly or indirectly by various mechanisms. Based on our testing of Macugen to date and our review of the carcinogenic potential of Macugen with an independent advisory board engaged by us, we believe that Macugen poses a low carcinogenicity risk. Further, as part of our approval process with the FDA for the use of Macugen in the treatment of neovascular AMD, we were not required to conduct further carcinogenicity testing of Macugen. We do not currently anticipate that we will be required to conduct additional carcinogenicity testing of Macugen prior to any approval of Macugen's use in the treatment of DME.

Before approving an application, the FDA may inspect the facility or the facilities at which the product is manufactured. The FDA will not approve the product unless cGMP compliance is satisfactory. The FDA will issue an approval letter if it determines that the application, manufacturing process and manufacturing facilities are acceptable. If the FDA determines the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals, which could delay or preclude us from marketing our products. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of the products. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval.

After regulatory approval of a product is obtained, we may be required to comply with a number of post-approval requirements, such as post-marketing testing and surveillance to monitor manufacturing controls or the product's safety or efficacy. For example, as part of the FDA's approval of Macugen, the FDA asked us to:

- provide subsequent information on the potential degenerative effects on the neurosensory retina based on a study of at least two years and adverse effects on the corneal endothelium based on a study of at least one year;
- provide safety and efficacy data from a clinical study of at least two years and of at least two additional doses of Macugen below the approved dose of 0.3 mg for neovascular AMD; and
- strengthen controls relative to the Macugen packaging components and operations.

In addition, holders of an approved NDA or BLA are required to report certain adverse reactions and production problems to the FDA, to provide updated safety and efficacy information and to comply with requirements concerning advertising and promotional labeling for their products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes certain procedural and documentation requirements. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We intend to invest in appropriate infrastructure at the manufacturing facility that we acquired in Boulder, Colorado in late 2004, to prepare the facility to become a second source for commercial scale production of the active pharmaceutical ingredient for Macugen. We use, and will continue to use in at least the near term, third party manufacturers to produce our products in clinical and commercial quantities. Future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract

manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product or the failure to comply with requirements may result in restrictions on a product, manufacturer or holder of an approved NDA or BLA, including withdrawal or recall of the product from the market or other voluntary or FDA-initiated action that could delay further marketing. Also, new government requirements may be established that could delay or prevent regulatory approval of our products under development.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products, including Macugen. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of foreign countries 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 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.

Outside the United States, Pfizer is responsible for seeking regulatory approvals of Macugen. Pfizer has filed new drug applications for Macugen with the European Medicines Agency, which covers 25 countries, and an additional six countries. In July 2004, the Pfizer-led bridging trial for the use of Macugen in the treatment of neovascular AMD began in Japan.

Third Party Reimbursement and Pricing Controls

General

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

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

Medicare

In December 2003, President Bush signed into law the MMA, new Medicare prescription drug coverage legislation that includes provisions that changed Medicare payment for physician-administered drugs. Effective January 2005, reimbursement for drugs is limited to an amount equal to a statutorily defined manufacturer's average sale price plus 6%. The definition of manufacturer's average sale price is intended to lead to lower levels of reimbursement to physicians than previously provided under the average wholesale price method. In addition, starting in January 2006, the MMA directs the Secretary of the Department of Health

and Human Services, or HHS, to contract with procurement organizations to purchase physician-administered drugs from the manufacturers and provides physicians with the option to obtain drugs through these organizations as an alternative to purchasing from the manufacturers, which some physicians may find advantageous.

These changes in reimbursements under MMA may reduce our potential revenues as a result of two principal factors. First, because physicians will receive lower levels of reimbursement under the manufacturer's average sale price methodology than under the current average wholesale price methodology, physicians may be less likely to purchase Macugen directly and more likely to obtain the product through procurement organizations. Second, the negotiated payment that we receive from procurement organizations may be less than the amount that we could otherwise have obtained from sales to physicians.

We currently market Macugen to physicians for use in the treatment of neovascular AMD. We expect that in the United States a majority of the patients who are treated with Macugen for neovascular AMD will be Medicare beneficiaries. The Centers for Medicare & Medicaid Services, or CMS, is the agency within the HHS, that administers Medicare and is responsible for reimbursement of the cost of Macugen when administered to Medicare beneficiaries and for the cost of physician services for administering the drug.

In general, Medicare makes separate payment to the physician or other purchaser for drugs, such as Macugen, that meet statutorily covered requirements, are not usually self-administered and are furnished by physicians in the office or in other outpatient settings. In February 2005, CMS determined that, effective January 1, 2005, Macugen's Medicare reimbursement will be average sales price (ASP) plus 6%. Macugen will be covered by Medicare when administered in the physician office unless CMS or a local Medicare contractor subsequently decides not to cover it. CMS has asserted the authority of Medicare not to cover particular drugs if it determines that they are not "reasonable and necessary" for Medicare beneficiaries.

CMS may create a national coverage determination for a product, which establishes on a nationwide basis the indications that will be covered and the frequency limits for administration of the product. However, for most new drugs that are eligible for payment, CMS does not create a national coverage determination. We do not know whether or not CMS will deem it appropriate to create a national coverage determination for Macugen or our other potential products. When there is no national coverage decision, the local Medicare contractors who are responsible for administering the program on a state by state basis have the discretion to issue local coverage decisions. These policies can include both coverage criteria for the drug and frequency limits for the administration of the drug and for ancillary services, such as diagnostics and imaging. The local contractors in different areas of the country may establish varying coverage criteria and frequency limits for Macugen. Medicare carriers of all 50 states have confirmed Macugen reimbursement, according to the FDA label, without restrictions. However, carriers may decide to create restrictive guidelines in the future.

In addition to payment for the drug itself, CMS also reimburses physicians for administering the product to Medicare beneficiaries. Medicare payment for physician services is determined according to a prospectively set payment rate, determined by a procedure code established by the American Medical Association. These codes, called Current Procedural Terminology, or CPT, codes, describe the procedure performed, but generally are not drug specific. Payors have recognized an existing CPT code to describe the procedure for administering Macugen, however reimbursement acceptance may change which may effect physicians' willingness to perform the procedure.

Commercial Insurers' Payment for Physician-Administered Drugs

Commercial insurers usually offer two types of benefits — medical benefits and pharmacy benefits. In most private insurance plans, physician-administered injectable drugs, such as Macugen, are provided under the medical benefit. If private insurers decide to cover Macugen, they will reimburse for the drug in a variety of ways depending on the particular insurance plan and the contract that the plan has negotiated with physicians. Like Medicare, commercial insurers have the authority to place coverage and utilization limits on physician-administered drugs. In response to the recent prescription drug coverage legislation that could result in reduced Medicare payment for physician-administered drugs, private insurers may adopt similar reduced payment amounts.

Employees

We believe that our continued success will depend greatly on our ability to identify, attract and retain capable employees. On March 1, 2005, we had 322 full time employees, including a total of 66 employees who hold either M.D. or Ph.D. degrees, or both. Our employees are not represented by any collective bargaining unit, and we believe our relations with our employees are good.

Recruiting and retaining qualified scientific personnel to perform research and development work in the future will also be critical to our success. We face the risk that we may not be able to attract and retain personnel on acceptable terms given the competition among biotechnology, pharmaceutical and health care companies, universities and non profit research institutions. In addition we rely on member of our Scientific Advisory Board and a significant number of consultants to assist us in formulating our research and development strategies.

Trademarks

We own a total of 18 United States trademark applications, including Eyetech™, Eyetech Pharmaceuticals™, MAP™ and Macugen®. All are covered by pending applications for registration in the United States Patent and Trademark Office.

Access to Our Filings with the Securities and Exchange Commission

Our Internet address is *www.eyetech.com*. The information on our website is not a part of, or incorporated into, this Annual Report on Form 10-K. We make our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to those reports, filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 available, without charge, on our website as soon as reasonably practicable after they are filed electronically with, or otherwise furnished to, the Securities and Exchange Commission.

Item 2. *Properties*

As of March 1, 2005, we leased a total of approximately 194,000 square feet of office and laboratory space. Our leased properties are described below.

Property Location	Approximate Square Feet	Use	Lease Expiration Date
3 Times Square, New York, New York	62,000	Corporate, Clinical, Safety and Regulatory	November 2021
500 Seventh Avenue, New York, New York	16,700	Former office space	December 2010
Lexington, Massachusetts	46,700	Laboratory	October 2014
Woburn, Massachusetts	10,600	Laboratory	July 2007
Cedar Knolls, New Jersey	25,000	Laboratory	April 2008
Boulder, Colorado	33,000	Manufacturing facility in development	November 2007

We continue to seek to sublet our former corporate headquarters located at 500 Seventh Avenue, New York, New York. We are also seeking to sublet our Woburn, Massachusetts facility.

Item 3. *Legal Proceedings*

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

Item 4. *Submission of Matters to a Vote of Security Holders*

We did not submit any matters to our security holders in the quarter ended December 31, 2004.

PART II

Item 5. ***Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities***

Our common stock has been traded on the Nasdaq National Market System under the symbol "EYET" since our initial public offering on January 30, 2004. Prior to that time there was no established public trading market for our common stock. The closing sale price for our common stock on March 10, 2005, as reported by the Nasdaq National Market System, was $26.43. The following table sets forth the range of the high and low sales prices as reported on the Nasdaq National Market from January 30, 2004 through December 31, 2004.

	High	Low
Year Ended December 31, 2004		
January 30 through March 31	$37.15	$29.25
Second Quarter	$49.12	$30.08
Third Quarter	$45.50	$29.68
Fourth Quarter	$47.92	$34.11

As of March 10, 2005, there were approximately 440 stockholders of record of our common stock.

We have never declared or paid cash dividends on either our common stock or preferred stock. We currently intend to retain all of our future earnings to finance the growth and development of our business. We do not intend to pay cash dividends to our stockholders in the foreseeable future.

Item 6. *Selected Financial Data*

You should read the following selected financial information together with our consolidated financial statements and the related notes appearing at the end of this report and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this report. We have derived the statement of operations information for the years ended December 31, 2002, 2003 and 2004 and the balance sheet information as of December 31, 2003 and 2004 from our audited consolidated financial statements which are included in this report. We have derived the statement of operations information for the period from our inception to December 31, 2000 and for the year ended December 31, 2001 and the balance sheet information as of December 31, 2000, 2001 and 2002 from our audited consolidated financial statements, which are not included in this report. Our historical results for any prior or interim period are not necessarily indicative of results to be expected for a full fiscal year or for any future 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 automatic conversion of all outstanding shares of our convertible preferred stock into shares of our common stock effective upon the completion of our initial public offering, as if the conversion had occurred at the date of the original issuance.

	Period from February 9, 2000 (Date of Inception) to December 31, 2000	Year Ended December 31, 2001	2002	2003	2004
	(In thousands, except share and per share numbers)				
Consolidated Statement of Operations Information:					
Collaboration revenue					
License fees	$ —	$ —	$ —	$ 4,583	$ 5,723
Reimbursement of development costs	—	—	—	36,836	43,629
Total collaboration revenue	—	—	—	41,419	49,352
Operating expenses:					
Research and development	10,879	22,157	39,663	70,932	102,739
Sales and marketing	—	—	—	4,599	33,343
General and administrative	1,413	4,338	5,319	6,822	17,435
Total operating expenses	12,292	26,495	44,982	82,353	153,517
Loss from operations	(12,292)	(26,495)	(44,982)	(40,934)	(104,165)
Interest income	1,181	1,815	1,809	2,171	3,810
Interest expense	—	—	—	(248)	(151)
Loss before income taxes	(11,111)	(24,680)	(43,173)	(39,011)	(100,506)
Provision for income taxes	—	—	—	(1,688)	—
Net loss	(11,111)	(24,680)	(43,173)	(40,699)	(100,506)
Preferred stock accretion	(1,080)	(2,494)	(5,096)	(9,160)	(816)
Net loss attributable to common stockholders	$ (12,191)	$ (27,174)	$ (48,270)	$ (49,860)	$ (101,322)
Basic and diluted net loss attributable to common stockholders per share	$ (5.49)	$ (7.43)	$ (13.06)	$ (12.62)	$ (2.70)
Weighted average shares outstanding — basic and diluted	2,219,178	3,659,422	3,697,192	3,950,481	37,587,299
Pro forma basic and diluted net loss attributable to common stockholders per share (unaudited)				$ (1.77)	$ (2.56)
Pro forma weighted average shares outstanding — basic and diluted (unaudited)				28,094,165	39,651,420

	As of December 31,				
	2000	2001	2002	2003	2004
			(In thousands)		
Balance Sheet Information:					
Cash, cash equivalents and marketable securities	$ 24,012	$ 57,019	$ 69,151	$ 131,374	$ 211,495
Total assets	25,252	60,090	76,589	149,480	339,459
Deferred revenue, less current portion				(65,417)	(159,706)
Long-term capital lease obligations and redeemable convertible preferred stock	(33,433)	(88,458)	(145,980)	(186,545)	(1,255)
Accumulated deficit	(11,111)	(39,365)	(87,635)	(137,495)	(238,817)
Total stockholders' (deficit) equity	(8,981)	(34,327)	(78,036)	(123,006)	131,138

Item 7. *Management's Discussion and Analysis of Financial Condition and Results of Operations*

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing elsewhere in this report. Some of the information contained in this discussion and analysis or set forth elsewhere in this report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. See "Special Note Regarding Forward-Looking Statements". You should review the "Risk Factors that May Affect Results" section of this report 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 that specializes in the development and commercialization of novel therapeutics to treat diseases of the eye. We commenced operations in April 2000. Since our inception, we have generated significant losses. As of December 31, 2004, we had an accumulated deficit of $238.8 million.

In December 2002, we entered into agreements with Pfizer to jointly develop and commercialize Macugen. As a result of our collaboration with Pfizer, we ceased to be a development-stage company in February 2003. As of December 31, 2004, substantially all of our revenues have been generated from amortization of the non-refundable, license payments that we have received from Pfizer and reimbursement to us by Pfizer of a portion of the ongoing development costs for Macugen.

Under the terms of our collaboration agreements with Pfizer, Pfizer has funded and is obligated to continue to fund a majority of the ongoing development costs incurred pursuant to an agreed upon development plan covering the development of Macugen for AMD, DME, RVO and other agreed upon ophthalmic indications. Our agreements provide that we will co-promote Macugen with Pfizer in the United States through Pfizer's and our own sales forces, and that we will maintain the inventory and record as revenue all United States product sales. We and Pfizer will share in profits and losses from the sale of Macugen in the United States. Outside the United States, subject to regulatory approval, Pfizer will market the product under an exclusive license, for which we will receive royalty payments based on net sales.

Pfizer has made the following payments and investments to date under our collaboration:

- In February 2003, upon effectiveness of the collaboration arrangements, Pfizer paid us $100 million, consisting of a $75 million initial license fee and a $25 million equity investment;
- In February 2004, Pfizer purchased an additional $10 million of our common stock at the closing of our initial public offering;
- In September 2004, Pfizer paid us $10 million after the acceptance for review by the FDA of our new drug application for the use of Macugen in the treatment of neovascular AMD;

- In October 2004, Pfizer paid us $5.5 million after the European Medicines Agency's acceptance of the filing of Pfizer's marketing authorization application for Macugen for use in the treatment of neovascular AMD;
- In January 2005, Pfizer paid us a $90 million license fee after the approval in December 2004 by the FDA of Macugen for the treatment of neovascular AMD; and
- In February 2005, Pfizer purchased 344,000 shares of our common stock at a purchase price of approximately $43.60 per share for total proceeds of $15 million after the approval by the FDA of Macugen for the treatment of neovascular AMD.

In the future, Pfizer may be obligated to make additional payments to us under the following circumstances:

- Up to $90 million in additional payments based on the achievement of additional worldwide regulatory submissions and approvals; and
- Up to $450 million in payments based upon attainment of specified sales levels of Macugen.

For more information about our collaboration with Pfizer see above, "Business — Collaboration with Pfizer."

Outside the United States, Pfizer is responsible for seeking regulatory approvals of Macugen. Pfizer has filed new drug applications for Macugen with the European Medicines Agency, which covers 25 countries, and an additional six countries. In July 2004, the Pfizer-led bridging trial for the use of Macugen in the treatment of neovascular AMD began in Japan.

We expect to continue to invest significant resources on the development of Macugen and other product candidates as we continue to market and sell Macugen in the United States. We also plan to continue to invest in research for additional applications of Macugen and to develop new drugs and drug delivery technologies and in building the appropriate infrastructure to support our business. We plan to continue to evaluate possible acquisitions or licenses of rights to potential new drugs, drug targets and drug delivery technologies that would fit within our growth strategy.

In May 2004, we entered into a lease for new research and development space in Lexington, Massachusetts, that will increase our annual facilities expenses by $1.6 million. In November 2004, we acquired most of the assets related to an oligonucleotide manufacturing facility in Boulder, Colorado, which we plan to develop as a second-source for commercial scale production of the active pharmaceutical ingredient in Macugen. We anticipate that this will be a significant investment over the next 12 to 18 months. Accordingly, we will need to generate significant revenues to achieve and then maintain profitability.

Most of our expenditures to date have been for research and development activities and general and administrative expenses. Research and development expenses represent costs incurred for product acquisition, clinical trials and activities relating to regulatory filings and manufacturing development efforts. We outsource our foreign clinical trials activities to third parties to maximize efficiency and minimize our internal overhead. We also outsource our global manufacturing development, but anticipate investing in the establishment of internal manufacturing capacity for the active pharmaceutical ingredient in Macugen. We expense our research and development costs as they are incurred.

We anticipate that our revenues for the foreseeable future will result primarily from sales in the United States of Macugen for the treatment of neovascular AMD, the continued amortization of license fees and the reimbursement of a portion of our ongoing development costs for Macugen.

In December 2004, we received approval from the FDA to market Macugen in the United States for the treatment of neovascular AMD including all lesion subtypes and sizes. Macugen is the first and only FDA-approved therapy for the treatment of all types of neovascular AMD, without angiographic or demographic restrictions. We believe Macugen is a novel treatment that targets the underlying cause of the disease. We began selling Macugen in the United States in January 2005. We sell Macugen to a limited number of

specialty distributors who in turn sell Macugen to physicians, physician group practices, hospitals, federal government buying groups and clinics. Our list price for Macugen is $995 per injection.

We have a dedicated sales force promoting Macugen to our target audience, which comprises approximately 2,000 specialists that treat retinal disease in the United States. Our sales force consists of 60 people, covering sales, sales management, reimbursement issues and education of doctors. In addition, Pfizer has dedicated over 160 sales representatives to Macugen targeting both general ophthalmologists and the retinal specialists.

We estimate that a large percentage of the cost of Macugen will be covered through Medicare plans. Medicare carriers of all 50 states have confirmed Macugen reimbursement, according to the FDA label, without restrictions. Additionally, CMS has determined that effective as of January 1, 2005, the allowable reimbursement for Macugen will be the manufacturer's average sales price plus 6%.

Planned and Ongoing Clinical Programs

In order to expand our pipeline of products to treat diseases of the eye with unmet medical need, we are actively pursuing a strategy to develop new drugs internally and to license or otherwise acquire rights to potential new drugs from third parties. We are also seeking to develop internally and acquire rights to alternative mechanisms for delivering ophthalmic drugs to the back of the eye. For example, since April 2004, we have had a research and collaboration agreement with Archemix that allows us to develop their current pipeline of aptamers in the field of ophthalmology. This agreement also provides us with the ability to have Archemix select new aptamers against our targets included in the research program for further development by us in ophthalmology. The following points summarize our material ongoing and planned trials and activities related to Macugen:

- We are continuing our Phase 2/3 clinical trial studying Macugen in neovascular AMD to provide subsequent information on the potential degenerative effects on the neurosensory retina and adverse effects on the corneal endothelium.
- In the second half of 2005, we plan to start a DME Phase 2/3 clinical trial and our Phase 2 RVO clinical trial is currently enrolling patients. Both DME and RVO represent large unmet medical needs, where there is no approved pharmacological therapy.
- During the first quarter of 2006, we are planning to launch a Phase 4 clinical trial which will explore the safety and efficacy of the FDA approved 0.3 mg dose of Macugen versus two additional lower doses of Macugen in patients with subfoveal, neovascular AMD.
- Beginning in the second quarter of 2005, we are planning with Pfizer to conduct a Phase 4 combination trial with Macugen and Visudyne versus Macugen alone, to determine if patients with the predominantly classic form of AMD benefit from combination therapy.
- We are conducting a pre-clinical research effort on improving Macugen's drug delivery, which if successful, may ultimately enable us to simplify the treatment for AMD patients. In addition, if extended release Macugen is ultimately successful, it may enable us to pursue the large prophylactic market for dry AMD.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements as well as the reported revenues and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments related to revenue recognition. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the

carrying value of assets and liabilities that are not readily apparent from other sources. Our estimates would likely change if we used different assumptions or conditions and actual results may differ from our estimates.

Revenue Recognition

In connection with our collaboration with Pfizer, we are entitled to receive non-refundable license payments from Pfizer based on the achievement of certain events. We record deferred license revenue when all the contractual obligations related to a non-refundable payment have been satisfied. We are amortizing deferred license revenue ratably over our performance period. Our performance period with respect to our collaboration agreement is the effective life of the agreement, which was 15 years commencing in December 2002. Management estimates the performance period based upon critical factors contained within the agreement along with other relevant facts and circumstances. We periodically review our estimates, which could result in a change in the deferral period, and could impact the timing and the amount of revenue recognized.

We receive reimbursement from Pfizer of Pfizer's share of development costs for Macugen. In accordance with Emerging Issues Task Force ("EITF") Issue 01-14, "Income Statement Characterization of Reimbursements Received for "Out-of-Pocket" Expenses Incurred", we report the reimbursement as revenues because among other factors, we have the primary obligation to conduct all clinical studies associated with Macugen and bear risk for selection of and payment to vendors. We record as expense the costs incurred by Pfizer for which we are contractually liable to Pfizer. In future periods we may be liable for costs incurred that do not meet the criteria to be classified as revenue. We would record these costs as expenses.

We receive reimbursement from Pfizer for a portion of the costs associated with the purchase of certain equipment related to the development of Macugen. For these items, when we receive payment from Pfizer, we record the reimbursement as deferred equipment revenue and amortize it over the equipment's expected useful life.

Effective upon the commercial availability and launch of Macugen in January 2005, we plan to report revenue on a gross basis for sales in the United States. We have determined that our responsibilities under our agreements with Pfizer to manage and assume responsibilities for obtaining FDA approvals for Macugen, including our separate contractual relationships and responsibilities to our clinical development contractors and our interaction with monitors and patients, qualify us as "principal" under the criteria set forth in EITF Issue 99-19, "Reporting Gross Revenue as a Principal vs. Net as an Agent."

During the years ended December 31, 2003 and 2004, we recognized $4.6 million and $5.7 million, respectively, of license fee revenue. At December 31, 2004, we classified as current deferred revenue $13.7 million related to payments for licenses and equipment. The balance of $159.7 million is classified as long-term deferred revenue on our balance sheet with a remaining amortization period of 13 years and 1 month. In future periods, this deferred license fee revenue will be offset by the amortization of license fees paid in connection with the acquisition of Macugen and certain manufacturing technologies, which we are required to capitalize upon regulatory approval.

Manufacturing Development and Inventory

For all periods presented we expensed all of our manufacturing development and inventory costs as research and development. Upon regulatory approval of Macugen, we began capitalizing all costs associated with the manufacturing of Macugen. At December 31, 2004, we had not capitalized any inventory as all costs associated with Macugen's active pharmaceutical ingredient and work in process were expensed as research and development costs prior to the approval by the FDA of Macugen on December 17, 2004. There were no finished goods as of December 31, 2004.

Stock-based Compensation

Stock-based compensation charges represent the difference between the exercise price of options and restricted stock awards granted to employees and directors and the fair value of our common stock on the date of grant for financial statement purposes in accordance with Accounting Principles Board Opinion No. 25 and its related interpretations. We recognize this compensation charge over the vesting periods of the shares issuable upon exercise of options or the lapsing of restrictions on restricted shares granted.

We recorded deferred stock-based compensation related to stock options and restricted stock awards granted to employees and directors through December 31, 2004 of $11.8 million, net of related amortization expense of $6.8 million for the year ended December 31, 2004. We expect to amortize deferred stock-based compensation with respect to stock options and restricted stock awards granted through December 31, 2004 in future periods, including $4.9 million during 2005, $4.3 million during 2006, $2.4 million during 2007 and $0.2 million during 2008.

Accounting Pronouncements

On December 16, 2004, the Financial Accounting Standards Board ("FASB") issued Statement of Financial Accounting Standards No. 123 (revised 2004),"Share-Based Payments" ("SFAS No. 123(R)"). SFAS No. 123(R) will require companies to measure all employee stock-based compensation awards using a fair value method and record such expense in its consolidated financial statements. In addition, the adoption of SFAS No. 123(R) requires additional accounting and disclosure related to the income tax and cash flow effects resulting from share-based payment arrangements. SFAS No. 123(R) is effective for the reporting periods after June 15, 2005 and we will be required to implement the standard for the year ending December 31, 2005. We anticipate that the adoption of the modified prospective method of calculating expense as required by SFAS No. 123(R) will result in the recognition of between $12 million and $15 million in additional non-cash compensation in 2005.

Results of Operations

Years Ended December 31, 2003 and 2004

The following table identifies our collaboration revenue for each of our major categories, for the years ended December 31, 2003 and 2004.

Revenue

	Year Ended December 31,	
	2003	2004
Revenue from license fees	$ 4,583,337	$ 5,722,499
Revenue from reimbursement of research and development costs	36,835,829	43,629,406
Total	$41,419,166	$49,351,904

Revenue. Collaboration revenue increased 19% from $41.4 million for the year ended December 31, 2003 to $49.4 million for the year ended December 31, 2004. Revenue from license fees increased by $1.1 million due to amortization of higher deferred revenue balances and an additional month of amortization in 2004 versus 2003. Revenue from reimbursement of research and development costs increased by $6.8 million. This increase was primarily due to increased reimbursement of expenditures related to preparation of our manufacturing capabilities for the expected commercial launch of Macugen.

Research and Development Expenses. Research and development expenses increased from $70.9 million for the year ended December 31, 2003 to $102.7 million for the year ended December 31, 2004. The increase in research and development expenses of $31.8 million was attributable to an increase of $20.3 million related to the continued development of manufacturing capabilities and related costs, including additional staffing, pre-approval readiness, raw materials and other related costs, an increase of $12.8 million related to milestone payments incurred in connection with the filing of our NDA in the United States for

Macugen, the filing of the marketing approval application filed with the European Medicines Agency and payments in connection with the licensing of non-Macugen pipeline technologies from third parties, primarily Archemix, and an increase of $1.8 million relating to additional research and development resources. These increases in cost were partially offset by a $3.1 million reduction in expenditures related to our clinical trials for the use of Macugen in the treatment of AMD and DME. We anticipate that research and development expenses will continue to increase as we further advance Macugen to commercialization for additional uses and begin to devote additional resources to other research and development projects.

Sales and Marketing Expenses. Sales and marketing expenses increased from $4.6 million for the year ended December 31, 2003 to $33.3 million for the year ended December 31, 2004. The increase in sales and marketing expenses of $28.7 million was primarily related to $14.4 million in higher personnel expenses, relating to the hiring and training of the sales field force, and $14.3 million of promotional and pre-marketing expenses, including $7.4 million that was paid to Pfizer and $1.0 million incurred for patient assistance programs.

General and Administrative Expenses. General and administrative expenses increased from $6.8 million for the year ended December 31, 2003 to $17.4 million for the year ended December 31, 2004. The increase of $10.6 million resulted from a $4.5 million increase in expenses related to expanded personnel, facilities and infrastructure to support our growth and our Pfizer collaboration, a $3.5 million increase related to the cost of being a public company, comprised primarily of professional services fees and directors and officers liability insurance, and a $2.6 million charge related to our former New York headquarters and our Woburn, Massachusetts research facilities.

Interest Income. Interest income increased from $2.2 million in the year ended December 31, 2003 to $3.8 million in the year ended December 31, 2004 as a result of higher levels of cash and marketable securities available for investment during 2004.

Net Loss. Net loss attributable to common stockholders increased from $49.9 million for the year ended December 31, 2003 to $101.3 million in the same period of 2004. The increase of $51.4 million in net loss was primarily a result of $20.3 million of costs incurred for the continued development of manufacturing capabilities, $12.8 million of costs incurred in connection milestone and license payments and includes $9.7 million of non-cash stock compensation expense. Basic and diluted net loss per common share for the years ended December 31, was $2.70 in 2004, compared to $12.62 for the same period in 2003. Pro forma basic and diluted loss per common share for the year ended December 31, was $2.56 in 2004, compared to $1.77 for the same period in 2003. The pro forma basic and diluted loss per common share gives effect to the automatic conversion of our outstanding convertible preferred stock into shares of common stock upon completion of our initial public offering in February 2004.

Years Ended December 31, 2002 and 2003

Revenue. We recognized revenue of $41.4 million during 2003, consisting of $36.8 million from reimbursement of development costs and $4.6 million from the amortization of the initial non-refundable, up-front license payment that we received from Pfizer in connection with our collaboration. 2003 was the first year in which we generated revenue.

Research and Development Expenses. Research and development expenses increased 79% from $39.7 million for 2002 to $70.9 million for 2003. The increase in research and development expenses of $31.2 million was attributable to a $14.9 million increase from the expansion during 2003 of our Phase 2/3 pivotal clinical trials for the use of Macugen in the treatment of wet AMD, which became fully enrolled in August 2002, and related costs, an increase of $10.2 million relating to the continued development of manufacturing capabilities and related costs, an increase of $3.9 million relating to the addition of 51 research and development staff, an increase of $3.3 million relating to the opening of our laboratory facilities in Cedar Knolls, New Jersey and Woburn, Massachusetts and an increase of $0.9 million associated with the development of drug delivery technologies and related costs. These increases in cost were offset by a $2.0 million decrease in licensing fees and expenses related to development of drug delivery and manufacturing technologies.

Sales and Marketing Expenses. Sales and marketing expenses were $4.6 million for 2003. We had no sales and marketing expenses in 2002 or 2001. The sales and marketing expenses in 2003 reflect market research expenses and personnel expenses relating to Macugen.

General and Administrative Expenses. General and administrative expenses increased 29% from $5.3 million for 2002 to $6.8 million for 2003. The increase resulted from increased management and personnel expenses and increases in facilities and infrastructure needed to support our Pfizer collaboration and further development efforts.

Interest Income. Interest income increased from $1.8 million in 2002 to $2.2 million in 2003 as a result of a higher level of cash and marketable securities available for investment during 2003 compared to 2002.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception, we have financed our operations through public sales and private placements of our capital stock, the initial and subsequent license fee payments that we received from Pfizer as part of our Macugen collaboration, reimbursement of development costs from Pfizer and the receipt of interest income. Through December 31, 2004, we received net proceeds of $336.0 million from the issuance of shares of common stock, convertible preferred stock and warrants. In connection with our initial public offering, all shares of preferred stock and related warrants were converted to common stock prior to December 31, 2004. We have also received net proceeds from capital equipment financing of $2.4 million.

In February 2004, we completed an initial public offering of our common stock of 7,425,000 shares at a price of $21.00 per share, which included the underwriters' option to purchase additional shares. Net proceeds from our initial public offering after deducting underwriters' discounts and expenses were $142.9 million. In addition, 476,190 shares of common stock were purchased concurrently with the initial public offering by Pfizer for $10 million as part of its commitment under our collaboration.

We issued 5,073,435 warrants in connection with original issuances of preferred stock from April 2000 to August 2002 and the in-licensing of Macugen in April 2000. Prior to the closing of our initial public offering, 1,511,381 shares of preferred stock were issued in connection with warrant exercises providing $10.4 million in aggregate proceeds. An additional 1,867,124 shares of preferred stock were issued on a cashless basis to the holders of 2,728,721 preferred stock warrants, who surrendered 861,597 preferred stock warrants as payment for those shares. All outstanding shares of preferred stock, including those shares issued in connection with warrant exercises, were automatically converted to an equivalent number of shares of common stock upon the closing of our initial public offering. Additionally, warrants to purchase 833,333 shares of series B preferred stock converted to an equal number of warrants to purchase an equal number of shares of common stock upon the closing of the initial public offering. These warrants were exercised during the quarter ended March 31, 2004 on a cashless basis, resulting in the issuance of 680,509 shares of common stock in exchange for the surrender of warrants to purchase 152,824 shares of common stock. No warrants remain outstanding at December 31, 2004.

In connection with our collaboration with Pfizer, we received in 2003 a $25.0 million investment in our preferred stock and a $75.0 million initial license fee and subsequent license fee payments of $105.5 million, $90 million of which is accrued at December 31, 2004. Pfizer purchased an additional $10 million of our common stock at the closing of our initial public offering in February 2004 and $15 million of our common stock in February 2005 in connection with the regulatory approval of Macugen. Pfizer has also agreed generally to fund a majority of the ongoing development costs incurred pursuant to an agreed development plan covering the development of Macugen for AMD, DME, RVO and other agreed upon ophthalmic indications. These obligations of Pfizer are contingent upon the achievement of milestones and are currently our only committed external source of funds.

In June 2004, we completed a secondary public offering of our common stock. The secondary public offering consisted of the sale of 4,439,000 shares of common stock at a price of $38.50 per share, which included the underwriters' option to purchase additional shares. All shares were sold by existing stockholders,

including employees, and employees exercising options. Our shares outstanding increased by 106,735 shares after the offering as a result of the option exercises, which provided proceeds to us of $0.1 million. The costs associated with the offering, excluding underwriters' discounts and commissions, which were payable by the selling stockholders, were approximately $1.0 million and were paid by us.

As of December 31, 2004, we had $211.4 million in cash, cash equivalents and marketable securities. Also as of that date, we had pledged $5.9 million of restricted cash as collateral for letters of credit for certain of our leased facilities. We believe that our available cash, cash equivalents and marketable securities, together with expected license, milestone payments and reimbursements from Pfizer under our collaboration, revenues from product sales and interest income will be sufficient to fund anticipated levels of operations through at least the end of 2006. We had no material capital expenditures during the quarter ended December 31, 2004 and have not made any material capital commitments at December 31, 2004.

In November 2004, we acquired most of the assets of Transgenomic, Inc.'s oligonucleotide manufacturing facility in Boulder, Colorado for $3.0 million in cash and the assumption of certain operating and capital leases associated with the acquired facilities. These acquired assets were recorded at their purchase price in November 2004. We plan to invest significantly in appropriate infrastructure at this facility to develop the facility to become a second source for commercial scale production of the active pharmaceutical ingredient in Macugen.

Income Taxes

As of December 31, 2004, we had net operating loss carryforwards for federal income taxes of $174.8 million. The $90 million deferred license fee as of December 31, 2004 will not be recognized for tax purposes until 2005 and therefore did not affect our net operating loss carryforward. Our utilization of the net operating loss and tax credit carryforwards may be subject to annual limitations pursuant to Section 382 of the Internal Revenue Code, and similar state provisions, as a result of changes in our ownership structure. The annual limitations may result in the expiration of net operating losses and credits prior to utilization. If not utilized, federal net operating loss carryforwards will begin to expire in 2020. To date, we have not recognized the potential tax benefit of our net operating losses.

At December 31, 2004 we had deferred tax assets representing the benefit of net operating loss carryforwards, deferred license fees received and certain start-up costs capitalized for tax purposes. We did not record a benefit for the deferred tax assets because realization of the benefit was uncertain, and, accordingly, a full valuation allowance is provided to offset the deferred tax asset.

We have not recorded any provision for income taxes during the year ended December 31, 2004. For the year ended December 31, 2003, we incurred $1.7 million for the alternative minimum tax as a result of the receipt of license fees from Pfizer.

Cash Flows

For the year ended December 31, 2004, we used net cash of $66.5 million in operating activities. This consisted primarily of a net loss for the period of $100.5 million, offset by an increase in accounts payable and accrued expenses of $11.3 million, a net increase in deferred revenue and collaboration receivable of $13.6 million, an increase in other liabilities and a loss on lease terminations aggregating $6.5 million and $9.7 million in non-cash stock-based compensation. We used $78.0 million for investing activities for the year ended December 31, 2004, which consisted primarily of net purchases of marketable securities. We received net cash of $160.3 million from financing activities during the year ended December 31, 2004, principally relating to the issuance of common stock in our initial public offering and other issuances of common stock, resulting in net proceeds, after transaction costs, of $158.4 million, and the issuance of convertible preferred stock upon the exercise of warrants for net proceeds of $2.6 million, offset by the repayment of capital leases of $0.7 million.

Funding Requirements

We expect to devote substantial resources to continue our research and development efforts and to expand our sales, marketing and manufacturing programs associated with the commercialization and launch of Macugen for the treatment of neovascular AMD, other future products and other uses for Macugen. Our funding requirements will depend on numerous factors, including:

- the success of our collaboration with Pfizer to develop and commercialize Macugen;
- the scope and results of our clinical trials;
- the cost of manufacturing activities;
- the cost of commercialization activities, including product marketing, sales and distribution;
- advancement of other product candidates into development;
- potential acquisition or in-licensing of other products or technologies;
- the timing of, extent of, and the costs involved in, obtaining regulatory approvals;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims and other patent-related costs, including litigation costs and the results of such litigation; and
- our ability to establish and maintain additional collaborative arrangements.

We believe that the key factors that will affect our internal and external sources of cash are:

- our ability to commercially launch Macugen in the United States and to obtain marketing approval outside the United States;
- the receptivity of the capital markets to financings by biotechnology companies;
- the success of our other preclinical and clinical development programs; and
- our ability to enter into additional strategic collaborations with corporate and academic collaborators and the success of such collaborations.

If our existing resources are insufficient to satisfy our liquidity requirements or if we acquire or license rights to additional product candidates, we may need to raise additional external funds through the sale of additional equity or debt securities. The sale of additional equity securities may result in additional dilution to our stockholders. Additional financing may not be available in amounts or on terms acceptable to us or at all. If we are unable to obtain additional financing, we may be required to reduce the scope of, delay or eliminate some or all of our planned business expansion, research, development and commercialization activities, which could harm our financial condition and operating results.

Contractual Obligations

Our major outstanding contractual obligations relate to our capital leases from equipment financings, facilities leases and obligations under a number of our collaboration and alliance agreements to pay milestone payments and royalties to the other parties to these agreements.

We have summarized in the table below our fixed contractual cash obligations as of December 31, 2004.

	Payments Due by Period				
Contractual Obligations	Total	Less Than One Year	One to Three Years	Three to Five Years	More Than Five Years
Capital lease obligations, including interest	$ 2,954,901	$1,625,844	$ 1,329,057	$ —	$ —
Operating leases	79,120,905	3,903,770	11,111,321	10,096,948	54,008,866
Total contractual cash obligations	$82,075,806	$5,529,614	$12,440,378	$10,096,948	$54,008,866

Under our agreements with Gilead Sciences, Inc., Nektar Therapeutics, and Isis Pharmaceuticals, Inc., we are obligated to make payments aggregating up to $36.3 million, of which $10.5 million has been expensed through December 31, 2004 and $6.0 million has been accrued at December 31, 2004, upon achieving specified milestones relating to the development and regulatory approval of Macugen and to pay royalties based on net sales of Macugen. The $6.0 million accrued at December 31, 2004 includes $3.0 million of prepaid royalties and $3.0 million that will be capitalized and amortized ratably over the remaining life of the agreements along with all payments made in connection with the achievement of future milestones. Future events that trigger the milestone payments include filing of an NDA with the FDA, making similar filings with foreign regulatory authorities, receiving marketing approval for Macugen by the FDA or similar foreign regulatory authorities and the first commercial sale of Macugen in various countries. These contingent milestone and royalty payment obligations are not included in the above table. The above table also excludes approximately $2.0 million in minimum fixed site fees payable to one of our contract manufacturers on a quarterly basis.

In January 2004, we entered into a sub-sublease arrangement for new corporate headquarters, clinical, safety and regulatory space in New York City. Our rent expense under that sub-sublease was $3.2 million in 2004. However, due to 2004 rent abatements, our cash expenditures for this property in 2004 were approximately $0.1 million. As security for the sub-sublease, we have named the sub-landlord as beneficiary under a secured bank letter of credit in the amount of $3.0 million, which is included in restricted cash on the balance sheet.

We have not subleased our former corporate offices at 500 Seventh Avenue, New York, New York, and as a result, under generally accepted accounting principles we have assessed the recoverability of the carrying value of our lease. We have determined that the amounts due under the lease will not be recoverable, and have recorded a loss in connection with this lease. A loss of $1.5 million was recorded in the second quarter of 2004 and was re-evaluated at December 31, 2004, resulting in an additional loss of $0.4 million; the loss includes the writedown of certain office equipment. In connection with our cessation of use of this facility, we had previously accelerated the recognition of amortization and depreciation expenses in connection with certain leasehold improvements and furniture and fixtures used at this facility. This resulted in an increase of $0.3 million to amortization and depreciation expense during the year ended December 31, 2004.

In May 2004, we entered into a lease agreement for new research and development space to replace our Woburn research facility. Payments related to this new space are included in the contractual obligations table above and are expected to result in approximately $1.6 million of additional expense annually. We have not been able to sublease our space in Woburn and as a result, we have been required under generally accepted accounting principles to assess the recoverability of the carrying value of our lease. We have determined that the amounts due under the lease will not be recoverable, and have recorded a loss in connection with this lease. The loss recorded at December 31, 2004 was approximately $0.8 million and was recorded during the fourth quarter of 2004. We will continue to re-evaluate the recoverability of this lease and may be required to record additional expense of up to $0.3 million in future periods.

RISK FACTORS THAT MAY AFFECT RESULTS

Risks Relating to Our Business

We depend heavily on the success of our one product, Macugen, which the FDA recently approved for use in the treatment of neovascular AMD.

In December 2004, the FDA granted marketing approval for the use of our first product, Macugen, in the treatment of neovascular AMD. We began selling Macugen in the United States in January 2005. Our ability to generate product revenues in the foreseeable future will depend solely on the commercialization of Macugen. The commercial success of Macugen will depend on several factors, including the following:

- acceptance of the product in the medical community, by patients receiving therapy and by third party payors;
- supplying sufficient quantities of Macugen to meet anticipated market;
- successfully building and sustaining manufacturing capacity to meet anticipated future demand;
- the competitive landscape for approved and developing therapies that will compete with Macugen;
- receipt of marketing approvals from non-U.S. regulatory authorities;
- our ability to expand the indications for which we can market Macugen;
- continued positive data from our clinical trials; and
- implementation of our post-approval commitments to the FDA in a timely fashion.

We depend heavily on our collaboration with Pfizer, which involves a complex sharing of control over decisions, responsibilities and costs and benefits. Any loss of Pfizer as a collaborator, or adverse development in the collaboration, would materially harm our business.

In December 2002, we entered into our collaboration with Pfizer to develop and commercialize Macugen for the prevention and treatment of diseases of the eye. The collaboration involves a complex sharing of control over decisions, responsibilities and costs and benefits. For example, with respect to the sharing of costs and benefits, Pfizer will co-promote Macugen with us in the United States and will share with us in profits and losses. Outside the United States, Pfizer will commercialize Macugen pursuant to an exclusive license and pay us a royalty on net sales. In addition, Pfizer generally is required to fund a majority of ongoing development costs incurred pursuant to an agreed upon development plan. Our collaboration is governed by a joint operating committee, consisting of an equal number of representatives of Pfizer and us who control decisions and responsibilities. There are also subcommittees with equal representation from both parties that have responsibility over development, regulatory, manufacturing and commercialization matters.

Ultimate decision-making authority is vested in us as to some matters and in Pfizer as to other matters. A third category of decisions requires the approval of both Pfizer and us. Outside the United States, ultimate decision-making authority as to most matters is vested in Pfizer. Pfizer may terminate the collaboration relationship without cause upon six to twelve months' prior notice, depending on when such notice is given. Any loss of Pfizer as a collaborator in the development or commercialization of Macugen, dispute over the terms of, or decisions regarding, the collaboration or other adverse development in our relationship with Pfizer would materially harm our business and might accelerate our need for additional capital.

Our product revenues are substantially dependent on a limited number of wholesale distributors to which we plan to sell Macugen. Product revenues may fluctuate from quarter to quarter based on the buying patterns of these distributors.

We sell Macugen primarily to three national pharmaceutical wholesale distributors located throughout the United States: McKesson Specialty, Priority Healthcare and Besse Medical. Our reliance on this small number of wholesalers could cause our revenues to fluctuate from quarter to quarter based on the buying

patterns of these wholesalers. In addition, if any of these wholesalers fails to pay us on a timely basis or at all, our financial position and results of operations could be materially adversely affected.

We face substantial competition with respect to sales of Macugen or other drugs that we may develop or commercialize, which may result in others discovering, developing or commercializing competing products before or more successfully than we do.

The commercialization and development of new drugs is highly competitive. We will face competition with respect to Macugen and any products we may commercialize or develop in the future from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Our competitors may develop products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

Macugen competes against two therapies for the treatment of neovascular AMD: photodynamic therapy, which was developed by QLT, Inc. and is marketed by Novartis AG, and thermal laser treatment. In the United States, photodynamic therapy is FDA-approved only for the predominantly classic subtype of neovascular AMD, which we estimate to represent 25% of the market for subfoveal neovascular AMD. In the European Union, the only approved therapy is photodynamic therapy, which is approved only for the predominantly classic and occult subtypes. In the United States, however, the Centers for Medicare & Medicaid Services implemented a decision in April 2004 to provide coverage for photodynamic therapy to patients with neovascular AMD who have occult and minimally classic lesions that are four disc areas or less in size and show evidence of recent disease progression even though the FDA has not approved photodynamic therapy for such treatment. The current therapies for the treatment of DME are thermal laser treatment and steroid treatment administered by physicians on an off-label basis. Unless additional therapies are approved, these existing therapies would represent the principal competition for Macugen in neovascular AMD and, if Macugen is approved for DME, for DME.

Additional treatments for AMD and DME are in various stages of preclinical or clinical testing. If approved, these treatments would also compete with Macugen. Potential treatments in late stage clinical trials include drugs sponsored by a collaboration of Genentech, Inc. and Novartis, Alcon, Inc., Allergan, Inc. through its acquisition of Oculex Pharmaceuticals, Inc., Eli Lilly and Co., Bausch & Lomb Incorporated, Regeneron Pharmaceuticals, Inc., Miravant Medical Technologies, Genaera Corporation and Sirna Therapeutics, Inc. Potential treatments in early stage clinical trials include drugs sponsored by Acuity Pharmaceuticals, Inc. and Pfizer. Some of the sponsors of these potential products have announced favorable results from Phase 1 or Phase 2 clinical trials. The Genentech/Novartis collaboration is developing an anti-VEGF humanized antibody fragment for intravitreal injection. This product candidate may be viewed as particularly competitive with Macugen because of the similarity of its mechanism of action. Preliminary results of Phase 3 clinical trials for this product candidate will likely be released this year. In addition, Alcon recently announced results of its Phase 3 clinical trial of anecortave acetate, an angiostatic compound, for the treatment of neovascular AMD patients, that features a less invasive injectable delivery that requires less frequent administration (every six months). Alcon has received fast track, Pilot 1 program designation from the FDA and has announced that it expects an FDA decision on its NDA in May 2005. Further, Alcon is enrolling patients in two Phase 3 clinical trials, one in South America and one in Europe, comparing the safety and efficacy of Alcon's compound against placebo in patients with all subtypes of neovascular AMD. Alcon also has initiated a five year Phase 3 risk reduction trial for the prevention of neovascular AMD. Other laser, surgical or pharmaceutical treatments for AMD and DME may also compete against Macugen. These competitive therapies may affect product pricing even if Macugen is otherwise viewed as a preferable therapy. Future competitive products may have superior efficacy, improved safety and convenience or reduced frequency of administration compared to Macugen. Because Macugen is currently our only approved product, any product that arises with superior efficacy, improved safety and convenience or reduced frequency of administration compared to Macugen may have a material adverse affect on our business. Even the expectation that a competitive product may gain marketing approval to compete with Macugen may have a negative effect on the trading price of our common stock.

Many of our competitors have substantially greater financial, technical and human resources than we have. Additional mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated by our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields.

There may be limited market acceptance of Macugen and other products we may develop in the future that are based on new technologies.

The commercial success of the products for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon the acceptance of these products by the medical community and third party payors as clinically useful, cost-effective and safe. Even if a potential product displays a favorable efficacy and safety profile in clinical trials, market acceptance of the product will not be known until some time after it is commercially launched. We expect that many of the products that we develop will be based upon new technologies. For example, Macugen is partially composed of a chemically synthesized aptamer, which is a type of nucleic acid, and is the first aptamer to be approved as a pharmaceutical by the FDA. As a result, it may be more difficult for us to achieve market acceptance of Macugen. Our efforts to educate the medical community about these potentially unique approaches may require greater resources than would be typically required for products based on conventional technologies. The safety, efficacy, convenience and cost-effectiveness of our products as compared to competitive products will also affect market acceptance.

We have only recently established our sales and marketing capabilities and have never marketed or sold products as a company. We will need to work with our partner, Pfizer, and integrate our marketing and sales infrastructures to successfully commercialize any products that we may develop, acquire or license.

We have limited experience as a company in marketing and selling products. We have a marketing team and specialty sales force with significant industry experience that began to market and sell Macugen in the United States in January 2005 in collaboration with Pfizer. To achieve commercial success for Macugen, our sales and marketing organization must work with our partner, Pfizer, to effectively integrate our sales and marketing infrastructures and implement our sales and marketing efforts. If our sales and marketing efforts are not successful our business will materially suffer.

We may not be successful in our efforts to expand our portfolio of products.

A key element of our strategy is to commercialize a portfolio of new ophthalmic drugs in addition to Macugen. We are seeking to do so through our internal research programs and through licensing or otherwise acquiring the rights to potential new drugs and drug targets for the treatment of ophthalmic disease.

A significant portion of the research that we are conducting involves new and unproven technologies. Research programs to identify new disease targets and product candidates require substantial technical, financial and human resources whether or not we ultimately identify any candidates. Our 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 they are unlikely to be effective drugs.

We may be unable to license or acquire suitable product candidates or products from third parties for a number of reasons. In particular, the licensing and acquisition of pharmaceutical products is a competitive area. A number of more established companies are also pursuing strategies to license or acquire products in the ophthalmic field. These established companies may have a competitive advantage over us due to their size,

cash resources and greater clinical development and commercialization capabilities. Other factors that may prevent us from licensing or otherwise acquiring suitable product candidates include the following:

- we may be unable to license or acquire the relevant technology on terms that would allow us to make an appropriate return from the product;
- companies that perceive us to be their competitors may be unwilling to assign or license their product rights to us; or
- we may be unable to identify suitable products or product candidates within our areas of expertise.

If we are unable to develop suitable potential product candidates through internal research programs or by obtaining rights to novel therapeutics from third parties, our business will suffer.

We expect to depend on collaborations with third parties to develop and commercialize our products.

Our business strategy includes entering into collaborations with corporate and academic collaborators for the research, development and commercialization of additional product candidates, such as our collaborations with Pfizer and Archemix. These arrangements may not be scientifically or commercially successful. The termination of any of these arrangements might adversely affect our ability to develop, commercialize and market our products.

The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Our collaborators will have significant discretion in determining the efforts and resources that they will apply to these collaborations. The risks that we face in connection with these collaborations, including our collaboration with Pfizer, include the following:

- our collaboration agreements are, or are expected to be, for fixed terms and subject to termination under various circumstances, including, in many cases, on short notice without cause;
- we expect to be required in our collaboration agreements not to conduct specified types of research and development in the field that is the subject of the collaboration. These agreements may have the effect of limiting the areas of research and development that we may pursue, either alone or in cooperation with third parties;
- our collaborators may develop and commercialize, either alone or with others, products and services that are similar to or competitive with our products that are the subject of the collaboration with us; and
- our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities following mergers and consolidations, which have been common in recent years in these industries. The ability of our products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products.

Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. Such terminations or expirations can adversely affect us financially as well as harm our business reputation.

We may not be successful in establishing additional collaborations, which could adversely affect our ability to develop and commercialize products and services.

An important element of our business strategy is entering into collaborations for the development and commercialization of products when we believe that doing so will maximize product value. If we are unable to reach agreements with suitable collaborators, we may fail to meet our business objectives for the affected product or program. We face significant competition in seeking appropriate collaborators. Moreover, these collaboration arrangements are complex to negotiate and time consuming to document. We may not be successful in our efforts to establish additional collaborations or other alternative arrangements. The terms of

any additional collaborations or other arrangements that we establish may not be favorable to us. Moreover, these collaborations or other arrangements may not be successful.

We currently have no operational manufacturing facilities and a limited number of manufacturing personnel. We will depend on third parties to manufacture Macugen and future products. If these manufacturers fail to meet our requirements, our product development and commercialization efforts may be materially harmed.

We have a limited number of personnel with experience in, and we do not own or lease operating facilities for, manufacturing any products. In November 2004, we acquired a manufacturing facility in Boulder, Colorado that we plan to develop to use as a second source of supply for the active pharmaceutical ingredient of Macugen, but that facility is not currently operational for such purpose. Accordingly, unless or until we develop or acquire manufacturing capabilities, we will depend on third parties to manufacture Macugen and any future products that we may develop.

We rely on separate single sources for the active pharmaceutical ingredient used in Macugen, the fill and finish for the finished drug product and the PEGylation reagent. While such suppliers and services providers provided similar products and services for our clinical trials and are providing services for our current commercial supply of Macugen, there is no assurance that these manufacturers will continue meet our requirements. Other sources for these products and services could be available to us, but we may be on terms less favorable to us and may delay our manufacturing activities.

In order to sustain Macugen supply at the quantities we believe will be necessary to meet anticipated future market demand, we and our contract manufacturer will need to increase the manufacturing capacity for the active pharmaceutical ingredient of Macugen. We believe we will have sufficient capacity to supply the active pharmaceutical ingredient and to manufacture Macugen to meet anticipated demand through the first quarter of 2007. We initially intend to increase manufacturing capacity for the active pharmaceutical ingredient of Macugen by duplicating a portion of our manufacturing lines at the contract manufacturer's facility. We also intend to invest in appropriate infrastructure our Boulder manufacturing facility to prepare the facility to become a second source for commercial scale production of the active pharmaceutical ingredient of Macugen. We will also continue to explore other alternatives for increasing manufacturing capacity. We are also investing to increase the capacity for finished product manufacturing and to improve the related packaging operation. If we are unable to increase our manufacturing capacity or are delayed in doing so, we may not be able to produce Macugen in a sufficient quantity to meet future requirements to sustain supply of the product to meet anticipated future demand. In addition, the cost of increasing manufacturing capacity may be expensive. Our revenues and gross margins could be adversely affected by any inability to meet demand and the increased cost in increasing manufacturing capacity.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party because of factors beyond our control; and
- the possibility of termination or non-renewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us.

The manufacture and packaging of pharmaceutical products such as Macugen are subject to the requirements of the FDA and similar foreign regulatory bodies. If we or our third party manufacturers fail to satisfy these requirements, our product development and commercialization efforts may be materially harmed.

The manufacture and packaging of pharmaceutical products, such as Macugen and our future product candidates, are regulated by the FDA and similar foreign regulatory bodies and must be conducted in accordance with the FDA's current good manufacturing practices and comparable requirements of foreign

regulatory bodies. There are a limited number of manufacturers that operate under these current good manufacturing practices regulations who are both capable of manufacturing Macugen and willing to do so. Failure by us (including in connection with the development of our Boulder manufacturing facility) or our third party manufacturers to comply with applicable regulations, requirements, or guidelines could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect our business. For example, as part of our application filed by Pfizer for the use of Macugen in the treatment of AMD in Europe, the facilities used at each stage of the manufacturing process for Macugen may go through a pre-approval inspection like that which was required by the FDA.

Changes in the manufacturing process or procedure, including a change in the location where the product is manufactured or a change of a third party manufacturer, require prior FDA review and/or approval of the manufacturing process and procedures in accordance with the FDA's current good manufacturing practices. There are comparable foreign requirements. This review may be costly and time consuming and could delay or prevent the launch of a product or the use of a facility to manufacture a product. For example, if after the development of our Boulder manufacturing facility, we move the manufacturing of the active pharmaceutical ingredient for Macugen to our facility in Boulder and we cannot establish, to the satisfaction of the FDA, that the products manufactured at the new site are comparable to those manufactured at the initial site, we may not obtain or may be delayed in obtaining approval to manufacture the active pharmaceutical ingredient in Boulder. In addition, if we elect to manufacture products at the facility of another third party, we would need to ensure that the new facility and the manufacturing process are in substantial compliance with current good manufacturing practices. Any such change in facility would be subject to a pre-approval inspection by the FDA and would again require us to demonstrate product comparability to the FDA. Foreign regulatory agencies have similar requirements.

The FDA and similar foreign regulatory bodies may also implement new standards, or change their interpretation and enforcement of existing standards and requirements, for manufacture, packaging or testing of products at any time. If we are unable to comply, we may be subject to regulatory, civil actions or penalties which could significantly and adversely affect our business.

Macugen and our other potential products may not be commercially viable if we fail to obtain an adequate level of reimbursement for these products by Medicare and other third party payors. The markets for our products may also be limited by the indications for which their use may be reimbursed or the frequency in which they may be administered.

The availability and levels of reimbursement by governmental and other third party payors affect the market for products such as Macugen and others that we may develop. These third party payors continually attempt to contain or reduce the costs of healthcare by challenging the prices charged for medical products and services. In some foreign countries, particularly Canada and the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six to twelve months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our products, including Macugen, to other available therapies. If reimbursement for our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels, our business could be materially harmed.

Because most persons suffering from neovascular AMD are elderly, we expect that coverage for Macugen in the United States will be primarily through the Medicare program. Although drugs that are not usually self-administered are ordinarily covered by Medicare, the Medicare program has taken the position that it can decide not to cover particular drugs if it determines that they are not "reasonable and necessary" for Medicare beneficiaries. Limitations on coverage could also be imposed at the local Medicare carrier level or by fiscal intermediaries. In February 2005, CMS determined that, effective January 1, 2005, Macugen's Medicare reimbursement will be average sales price (ASP) plus 6 percent. As of February 28, 2005, Medicare carriers of all 50 states have confirmed Macugen reimbursement, according to the FDA label, without restrictions.

However, our business could be materially adversely affected if the Medicare program, local Medicare carriers or fiscal intermediaries were to subsequently make such a determination and deny or limit the reimbursement of Macugen. Our business also could be adversely affected if physicians are not reimbursed by Medicare for the cost of the procedure in which they administer Macugen on a basis satisfactory to the administering physicians. If the local contractors that administer the Medicare program are slow to reimburse physicians for Macugen, the physicians may pay us more slowly, which would adversely affect our working capital requirements.

We also will need to obtain approvals for reimbursement of Macugen from private insurers, including managed care organizations. We expect that private insurers will consider the efficacy, cost-effectiveness and safety of Macugen in determining whether and at what level to approve reimbursement for Macugen therapy. Obtaining these approvals can be a time consuming and expensive process. Our business would be materially adversely affected if we do not receive approval for reimbursement of Macugen from private insurers on a satisfactory basis.

Our business could also be adversely affected if the Medicare program or other reimbursing bodies or payors limit the indications for which Macugen will be reimbursed to a smaller set than we believe it is effective in treating or establish a limitation on the frequency with which Macugen may be administered that is less often than we believe would be effective.

We expect to experience pricing pressures in connection with the sale of Macugen and our future products due to the trend toward programs aimed at reducing healthcare costs, the increasing influence of health maintenance organizations and additional legislative proposals.

The 2003 Medicare prescription drug coverage legislation, The Medicare Prescription Drug Improvement and Modernization Act, or the MMA, and future legislative or regulatory reform of the healthcare system may affect our ability to sell our products profitably.

In both the United States and some non-U.S. jurisdictions, there have been a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. In the United States, new legislation may be proposed at the federal and state levels that would result in significant changes to the healthcare system, either nationally or at the state level. In December 2003, President Bush signed into law new Medicare prescription drug coverage legislation, the MMA. Effective January 2004, the legislation changed the methodology used to calculate reimbursement for drugs such as Macugen that are administered in physicians' offices in a manner intended to reduce the amount that is subject to reimbursement. In addition, beginning in January 2006, the legislation directs the Secretary of the Department of Health and Human Services, or HHS, to contract with procurement organizations to purchase physician-administered drugs from the manufacturers and provides physicians with the option to obtain drugs through these organizations as an alternative to purchasing from the manufacturers, which some physicians may find advantageous. These changes may also cause private insurers to reduce the amounts that they will pay for physician-administered drugs. In addition, CMS, the agency within HHS that administers Medicare and is responsible for reimbursement of the cost of Macugen, has asserted the authority of Medicare not to cover particular drugs if it determines that they are not "reasonable and necessary" for Medicare beneficiaries or to cover them at a lesser rate, comparable to that for drugs already reimbursed that CMS considers to be therapeutically comparable. Further federal and state proposals and healthcare reforms are likely. Our results of operations could be materially adversely affected by the Medicare prescription drug coverage legislation, by the possible effect of this legislation on amounts that private insurers will pay and by other healthcare reforms that may be enacted or adopted in the future.

We face the risk of product liability claims and may not have adequate insurance coverage.

Our business exposes us to the risk of product liability claims that is inherent in the manufacturing, testing and marketing of drugs and related products. Claims that one or more of our products harms people, regardless of the merits, could be costly, divert our management's attention and adversely affect our reputation and demand for our products.

We currently have product liability insurance that covers liability arising from our clinical trials and product sold up to a $20 million annual aggregate limit. Insurance coverage is increasingly expensive. We may not have and we may not be able to maintain adequate protection against potential liabilities. If we are unable to maintain insurance at acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which may materially and adversely affect our business and financial position. These liabilities could prevent or interfere with our product development and commercialization efforts.

We depend on our key personnel. If we are not able to retain them or recruit additional technical personnel, our business will suffer.

We are highly dependent on the principal members of our management and scientific staff, particularly Dr. David R. Guyer, our co-founder and Chief Executive Officer, and Dr. Anthony P. Adamis, our scientific pioneer, Chief Scientific Officer and Executive Vice President, Research and Development. Our employment agreements with these and our other executive officers are terminable on short or no notice. We do not carry key man life insurance on any of our key personnel. The loss of service of any of our key employees could harm our business.

In addition, our growth will require us to hire a significant number of qualified technical, commercial and administrative personnel. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we cannot continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow.

We are growing rapidly, and if we fail to adequately manage that growth, our business could be adversely impacted.

Our aggressive growth plan has included substantial and increasing investments in research and development, sales and marketing, and facilities. We plan to continue to grow, and our plan has a number of risks, some of which we cannot control. For example:

- we have a single source of product revenue, a fixed amount of cash and predetermined anticipated milestone payments that may be due to us, so we will need to generate significant and continued product or other revenues to cover our anticipated growing level of operating expenses;
- we will need to continue to assimilate a large number of new employees in different functions throughout the company;
- we will need to manage complexities associated with a larger and faster growing organization; and
- we will need to accurately anticipate demand for our products and maintain adequate manufacturing capacity, and our ability to do so may depend on factors that we do not control.

Of course, there may be other risks unknown to us and we cannot guarantee that we will be able to successfully manage these or other risks.

We depend on third parties in the conduct of our clinical trials for Macugen and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of our ongoing clinical trials for Macugen and expect to do so with respect to other product candidates. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the clinical investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The

failure of these third parties to carry out their obligations could delay or prevent the development and commercialization of additional indications for Macugen and future product candidates.

Regulatory Risks

If our clinical trials generate data that are not as favorable as historical data, our clinical trials are viewed as unsuccessful, or if we experience significant delays in these trials, our ability to further commercialize Macugen and our future product candidates will be impaired.

We must provide the FDA and similar foreign regulatory authorities with preclinical and clinical data that demonstrate that our product candidates are safe and effective for each target indication before they can be approved for commercial distribution. The preclinical testing and clinical trials of any product candidates that we develop must comply with regulations by numerous federal, state and local government authorities in the United States, principally the FDA, and by similar agencies in other countries. Clinical development is a long, expensive and uncertain process and is subject to delays. We may encounter delays or rejections based on our inability to enroll or keep enrolled enough patients to complete our clinical trials. Patient enrollment depends on many factors, including the size of the patient population, the nature of the trial protocol, the proximity of patients to clinical sites and the eligibility criteria for the study.

Our Phase 2/3 pivotal clinical trial for the use of Macugen in the treatment of wet AMD and Phase 2 clinical trial for use of Macugen in the treatment of DME are currently fully enrolled. We are also enrolling patients in our Phase 2 clinical trial for the use of Macugen in the treatment of RVO and we plan additional clinical trials in the future. We also may commence other additional clinical trials in the future. Although we have not to date experienced any significant delays in enrolling clinical trial patients for our ongoing clinical trials, delays in patient enrollment for future trials may result in increased costs and delays, which could have a harmful effect on our ability to develop products.

It may take several years to complete the testing of a product, and failure can occur at any stage of testing. For example:

- interim results of preclinical or clinical studies are not necessarily predictive of their final results, and acceptable results in early studies might not be seen in later studies, in large part because earlier phases of studies are often conducted on smaller groups of patients than later studies, and without the same trial design features, such as randomized controls and long-term patient follow-up and analysis;
- potential products that appear promising at early stages of development may ultimately fail for a number of reasons, including the possibility that the products may be ineffective, less effective than products of our competitors or cause harmful side effects;
- any preclinical or clinical test may fail to produce results satisfactory to the FDA or foreign regulatory authorities;
- preclinical and clinical data can be interpreted in different ways, which could delay, limit or prevent regulatory approval;
- negative or inconclusive results from a preclinical study or clinical trial or adverse medical events during a clinical trial could cause a preclinical study or clinical trial to be repeated or a program to be terminated, even if other studies or trials relating to the program are successful;
- the FDA can place a hold on a clinical trial if, among other reasons, it finds that patients enrolled in the trial are or would be exposed to an unreasonable and significant risk of illness or injury;
- we may encounter delays or rejections based on changes in regulatory agency policies during the period in which we develop a drug or the period required for review of any application for regulatory agency approval; and
- our clinical trials may not demonstrate the safety and efficacy needed for our products to receive regulatory approval.

In addition, as part of the drug approval process, we must conduct a comprehensive assessment of the carcinogenic, or cancer causing, potential of our product candidates. Our testing of Macugen to date indicates that the product's carcinogenic potential is low. As part of our approval process with the FDA for the use of Macugen in the treatment of neovascular AMD, we were not required to conduct further carcinogenicity testing of Macugen. We do not currently anticipate that we will be required to conduct additional carcinogenicity testing of Macugen prior to any approval of Macugen's use in the treatment of DME.

If we are required to conduct additional clinical trials or other studies of Macugen for use in the treatment of DME or RVO beyond those that we currently contemplate, if we are unable to successfully complete our clinical trials or other studies or if the results of these trials or studies are not positive or are only modestly positive, we may be delayed in obtaining marketing approval for Macugen for such indications, we may not be able to obtain marketing approval for such indications or we may obtain approval that is not as broad as intended. Our product development costs will also increase if we experience delays in testing or approvals. Significant clinical trial delays could allow our competitors to bring products to market before we do and impair our ability to commercialize our products or potential products. If any of this occurs, our business will be materially harmed.

Furthermore, our future products may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use, which could have a material adverse effect on our business. The FDA and other regulatory authorities may not approve any future product that we may develop. The FDA may not approve Macugen for any additional indications.

The "fast track" designation for development of Macugen in DME may not actually lead to a faster development or regulatory review or approval process.

If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA "fast track" designation. The fast track classification does not apply to the product alone, but applies to the combination of the product and the specific indication or indications for which it is being studied. The FDA's fast track programs are designed to facilitate the clinical development and evaluation of the drug's safety and efficacy for the fast track indication or indications. Marketing applications filed by sponsors of products in fast track development may qualify for expedited review under policies or procedures offered by the FDA, but the fast track designation does not assure such qualification.

We obtained, and received approval from the FDA after, a fast track designation from the FDA for Macugen in the treatment of neovascular AMD. We have also obtained a fast track designation from the FDA for Macugen for the treatment of DME. However, our fast track designation with respect to DME may be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical development program. Further, we may not experience a faster development process, review or approval with respect to any application we may file with respect to the use of Macugen in the treatment of DME compared to conventional FDA procedures.

We may not be able to obtain marketing approval for any other product resulting from our development efforts. Failure to obtain additional approvals could materially harm our business.

Although we were not required to conduct additional research and development prior to the approval of Macugen in the United States for the treatment of neovascular AMD, the use of Macugen for the treatment of other indications and other products that we are developing or may develop in the future will require additional research and development and regulatory approval prior to commercial launch. The research and development work that we must perform will include extensive preclinical studies and clinical trials. We will be required to obtain an investigational new drug application, or IND, prior to initiating human clinical trials in the United States and must obtain regulatory approval prior to any commercial distribution. This process is expensive, uncertain and lengthy, often taking a number of years until a product is approved for commercial distribution. While we have received regulatory approval to market Macugen in the United States for use in

the treatment of neovascular AMD, failure to obtain required regulatory approvals for other uses of Macugen or for other products could materially harm our business.

We may need to successfully address a number of technological challenges in order to complete the development of Macugen for other indications or any of our future products, such as manufacturing process validation and product specification testing.

In addition, administration of a drug via intravitreal injection is a new method for the potentially long-term treatment of chronic eye disease. As a result, as we experienced with the FDA prior to the approval of Macugen in the United States, regulatory agencies may apply new standards for safety, manufacturing, packaging and distribution of drugs using this mode of administration. It may be time consuming or expensive for us to comply with these standards. This could result in delays in our obtaining marketing approval for Macugen outside the United States, or possibly preclude us from obtaining such approval. This could also increase our commercialization costs, possibly materially.

Furthermore, our future products may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use, which could have a material adverse effect on our business. The FDA and other regulatory authorities may not approve any product that we develop.

Macugen and any future products could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements, or if we experience unanticipated problems with our products after approval.

Macugen, or any other product for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, advertising and promotional activities for such product, will be subject to continual requirements, review and periodic inspections by the FDA and other regulatory bodies. Even if regulatory approval of a product is granted, such as the FDA's approval of Macugen in December 2004 for the treatment of neovascular AMD, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. For example, as part of the FDA's approval of Macugen for use in the treatment of neovascular AMD, the FDA asked us to:

- provide subsequent information on the potential degenerative effects on the neurosensory retina based on a study of at least two years and adverse effects on the corneal endothelium based on a study of at least one year;
- provide safety and efficacy data from a clinical study of at least two years of at least two additional doses of Macugen below the approved dose of 0.3 mg for neovascular AMD; and
- strengthen controls relative to the Macugen packaging components and operations.

Furthermore, new information may arise from our ongoing or new clinical trials or continuing analysis of the data from our clinical trials that may be viewed as less favorable than previous data.

Later discovery of previously unknown problems with our products, manufacturer or manufacturing processes, or failure to comply with regulatory requirements, such as the post-approval commitments outlined above, may result in:

- restrictions on such products or manufacturing processes;
- withdrawal of the products from the market;
- voluntary or mandatory recall;
- fines;
- suspension of regulatory approvals;

- requests from the FDA or other agencies for additional information from us or data from additional clinical trials;
- product seizure; and
- injunctions or the imposition of civil or criminal penalties.

We may be slow to adapt, or we may never adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements or policies.

Failure to obtain regulatory approval in foreign jurisdictions would prevent us from marketing our products abroad.

We intend to have our products marketed outside the United States. In order to market our products in the European Union and many other non-U.S. jurisdictions, we must obtain separate regulatory approvals and comply with numerous and varying regulatory requirements. In the case of Macugen, Pfizer has responsibility to obtain regulatory approvals outside the United States, and we will depend on Pfizer to obtain these approvals. Pfizer has filed new drug applications for Macugen with the European Medicines Agency, which covers 25 countries, and with an additional six countries. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ from that required to obtain FDA approval. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. We and our collaborators may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market. The failure to obtain these approvals could materially adversely affect our business, financial condition and results of operations.

We have only limited experience in regulatory affairs, and some of our products may be based on new technologies. These factors may affect our ability or the time we require to obtain necessary regulatory approvals.

We have only limited experience as a company in filing and prosecuting the applications necessary to gain regulatory approvals. Moreover, some of the products that are likely to result from our product development, licensing and acquisition programs may be based on new technologies that have not been extensively tested in humans. The regulatory requirements governing these types of products may be less well defined or more rigorous than for conventional products. As a result, we may experience a longer regulatory review in connection with obtaining regulatory approvals of any products that we develop, license or acquire.

Risks Relating to Intellectual Property

If we are unable to obtain and maintain protection for the intellectual property incorporated into our products, the value of our technology and products will be adversely affected.

Our success will depend in large part on our ability or the ability of our licensors to obtain and maintain protection in the United States and other countries for the intellectual property incorporated into our products. The patent situation in the field of biotechnology and pharmaceuticals generally is highly uncertain and involves complex legal and scientific questions. Neither we nor our licensors may be able to obtain additional issued patents relating to our technology. Even if issued, patents may be challenged, narrowed, invalidated, or circumvented, which could limit our ability to stop competitors from marketing similar products or limit the length of term of patent protection we may have for our products. In addition, our patents and our licensors' patents also may not afford us protection against competitors with similar technology. Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make

the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

If we fail to comply with our obligations in the agreements under which we license development or commercialization rights to products or technology from third parties, we could lose license rights that are important to our business.

We are a party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we hold licenses from Gilead Sciences, Nektar Therapeutics and Isis Pharmaceuticals under patents relating to Macugen. These licenses impose various commercialization, 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 would not be able to market products, such as Macugen, that may be covered by the license.

If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and products could be adversely affected.

In addition to patented technology, we rely upon unpatented proprietary technology, processes, and know-how. We seek to protect this information in part by confidentiality agreements with our employees, consultants and third parties. These agreements may be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently developed by competitors.

Third parties may own or control patents or patent applications that could be determined to be infringed by our technologies, drug targets or potential products. This could cause us to become involved in expensive patent litigation or other proceedings, which could result in our incurring substantial costs and expenses and liability for damages. This could also require us to seek licenses, which could increase our development and commercialization costs. In either case, this could require us to stop some of our development and commercialization efforts.

We may not have rights under some patents or patent applications that could be determined to be infringed by technologies that we use in our research, drug targets that we select or product candidates that we seek to develop and commercialize. Third parties may own or control these patents and patent applications in the United States and abroad. These third parties could bring claims against us or our collaborators that would cause us to incur substantial expenses and, if successful against us, could cause us to pay substantial damages. Further, if a patent infringement suit were brought against us or our collaborators, we or they could be forced to stop or delay research, development, manufacturing or sales of the product or product candidate that is the subject of the suit.

As a result of patent infringement claims, or in order to avoid potential claims, we or our collaborators may choose to seek, or be required to seek, a license from the third party and would most likely be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we or our collaborators were able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations if, as a result of actual or threatened patent infringement claims, we or our collaborators are unable to enter into licenses on acceptable terms. This could harm our business significantly.

There has been substantial litigation and other proceedings regarding the patent and other intellectual property rights in the pharmaceutical and biotechnology industries. In addition to the possibility of infringement claims against us, we may become a party to other patent litigation and other proceedings, including interference proceedings declared by the United States Patent and Trademark Office and opposition proceedings in the European Patent Office, regarding intellectual property rights with respect to our products and technology. The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the costs of such litigation or proceedings more

effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

Risks Relating to Our Financial Results and Need for Financing

We have a limited operating history and have incurred losses since inception. If we do not generate significant revenues, we will not be able to achieve profitability.

Sales of Macugen in the United States are currently our only source of product revenue. We have a limited operating history and began selling Macugen in the United States in January 2005. To date, we have focused primarily on the development of Macugen and preparation for its commercialization. We began operations in 2000, and we have not been profitable in any quarter since inception. As of December 31, 2004, we had an accumulated deficit of approximately $238.8 million. We expect to increase our spending significantly as we continue to expand our infrastructure, development programs and commercialization activities. As a result, we will need to generate significant revenues to pay these costs and achieve profitability. We do not know whether or when we will become profitable because of the significant uncertainties with respect to our ability to generate revenues from the sale of our products and from our existing and potential future collaborations.

Our revenues and operating results may fluctuate, and this fluctuation could cause financial results to be below expectations.

Our operating results may fluctuate from period to period for a number of reasons. Even if we assume that revenues will continue to grow, some of our operating expenses are fixed in the short term. Because of this, even a relatively small revenue shortfall may cause a period's results to be below our expectations or projections. A revenue shortfall could arise from any number of factors, some of which we cannot control. For example, we may face:

- lower than expected demand for our products;
- inability to provide adequate supply of our products;
- changes in the government's or private payors' reimbursement policies for our products;
- changes in wholesaler buying patterns;
- increased competition from new or existing products;
- delays in approvals for new products;
- fluctuations in foreign currency exchange rates; and
- changes in our product pricing strategies.

We may need additional financing, which may be difficult to obtain. Our failure to obtain necessary financing or obtaining financing on unattractive terms could adversely affect our development programs and other operations.

We will require substantial funds to conduct development, including preclinical testing and clinical trials, of our potential products. We will also require substantial funds to meet our obligations to our licensors and maximize the prospective benefits to us from our licensors, and manufacture and market products that are approved for commercial sale in the future, including Macugen.

We currently believe that our available cash, cash equivalents and marketable securities, expected milestone payments and reimbursements from Pfizer under our collaboration and interest income will be

sufficient to fund our anticipated levels of operations through at least the end of 2006. However, our future capital requirements will depend on many factors, including:

- the success of our collaboration with Pfizer to commercialize and further develop Macugen;
- the scope and results of our clinical trials;
- advancement of other product candidates into development;
- potential acquisition or in-licensing of other products or technologies;
- the timing of, extent of, and the costs involved in, obtaining regulatory approvals;
- the cost of manufacturing activities;
- the cost of commercialization activities, including product marketing, sales and distribution;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims and other patent-related costs, including litigation costs and the results of such litigation; and
- our ability to establish and maintain additional collaborative arrangements.

Additional financing may not be available to us when we need it or it may not be available on favorable terms. If we are unable to obtain adequate financing on a timely basis, we may be required to significantly curtail one or more of our development, licensing or acquisition programs. We could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own. If we raise additional funds by issuing equity securities, our then-existing stockholders will experience dilution and the terms of any new equity securities may have preferences over our common stock.

General Company Related Risks

Our executive officers, directors and major stockholders will maintain the ability to control all matters submitted to stockholders for approval.

Our executive officers, directors and stockholders who own more than 5% of our outstanding common stock, in the aggregate, beneficially owned shares representing approximately 38% of our capital stock as of March 10, 2005. As a result, if these stockholders were to choose to act together, they would be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would substantially influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

Provisions in our charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us.

Provisions of our corporate charter and bylaws may 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 may also prevent or frustrate attempts by our stockholders to replace or remove our management. These provisions include:

- a classified board of directors;
- limitations on the removal of directors;
- advance notice requirements for stockholder proposals and nominations;
- the inability of stockholders to act by written consent or to call special meetings; and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

The affirmative vote of the holders of at least 75% of our shares of capital stock entitled to vote is necessary to amend or repeal the above provisions of our certificate of incorporation. In addition, absent approval of our board of directors, our bylaws may only be amended or repealed by the affirmative vote of the holders of at least 75% of our shares of capital stock entitled to vote.

In addition, Section 203 of the Delaware General Corporation Law prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns or within the last three years has owned 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner. Accordingly, Section 203 may discourage, delay or prevent a change in control of our company.

Our stock price is volatile; purchasers of our common stock could incur substantial losses.

Our stock price is volatile. From our initial public offering in January 2004 through March 10, 2005, the trading price of our common stock has ranged from $25.55 to $49.12 per share. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their common stock at or above their respective purchase prices. The market price for our common stock may be influenced by many factors, including:

- failure of Macugen or any of our product candidates, if approved, to achieve commercial success;
- results of our clinical trials or those of our competitors;
- the regulatory status of Macugen and our other potential products;
- the regulatory status of potentially competitive products;
- developments concerning our collaborators, including Pfizer;
- regulatory developments in, and outside of, the United States;
- developments or disputes concerning patents or other proprietary rights;
- our ability to manufacture products to commercial standards;
- public concern over our drugs;
- litigation;
- the departure of key personnel;
- future sales of our common stock;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- investors' perceptions of us; and
- general economic, industry and market conditions.

If there are substantial sales of our common stock, our stock price could decline.

If our existing stockholders sell a large number of shares of our common stock or the public market perceives that existing stockholders might sell shares of common stock, the market price of our common stock could decline significantly. All of the shares sold in our initial public offering in January 2004 and secondary public offering in May 2004 are freely tradable without restriction or further registration under the federal securities laws, unless purchased by our "affiliates" as that term is defined in Rule 144 under the Securities Act. Substantially all other shares of our common stock are saleable under Rule 144 under the Securities Act.

Also, some stockholders have rights with respect to the registration of the sale of their shares of common stock with the Securities and Exchange Commission.

We have registered approximately 9,543,000 shares of common stock that are authorized for issuance under our stock plans. As of December 31, 2004, 5,382,629 shares were subject to outstanding options and restricted stock grants, 4,066,302 of which were vested. Of the outstanding options, options for 2,998,863 shares were immediately exercisable, but we had the right to repurchase at the initial exercise price all but 1,490,855 of the shares issuable upon exercise of such options. Because they are registered, the shares authorized for issuance under our stock plans can be freely sold in the public market upon issuance, subject to our repurchase rights and the restrictions imposed on our affiliates under Rule 144.

Item 7A. ***Quantitative and Qualitative Disclosure About Market Risk***

Our exposure to market risk is confined to our cash, cash equivalents and marketable securities. We invest in high-quality financial instruments, primarily money market funds, federal agency notes, asset backed securities, corporate debt securities and United States treasury notes, with the effective duration of the portfolio less than nine months and no security with an effective duration in excess of two years, which we believe are subject to limited credit risk. We currently do not hedge interest rate exposure. Due to the short-term nature of our investments, we do not believe that we have any material exposure to interest rate risk arising from our investments.

Most of our transactions are conducted in United States dollars, although we do have some development and commercialization agreements with vendors located outside the United States. Transactions under certain of these agreements are conducted in United States dollars, subject to adjustment based on significant fluctuations in currency exchange rates. Transactions under certain other of these agreements are conducted in the local foreign currency. If the exchange rate undergoes a change of 10%, we do not believe that it would have a material impact on our results of operations or cash flows.

Item 8. ***Financial Statements and Supplementary Data***

Our financial statements are annexed to this report beginning on page F-1.

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

None

Item 9A. ***Controls and Procedures***

Disclosure controls and procedures are controls and other procedures that are designed to ensure that information required to be disclosed in our reports filed under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include controls and procedures designed to ensure that information required to be disclosed in our reports filed under the Exchange Act is accumulated and communicated to our management, including our chief executive officer and chief financial officer as appropriate, to allow timely decisions regarding required disclosure.

As required by Rule 13a-15 under the Exchange Act, as of the end of the period covered by this report, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. This evaluation was carried out under the supervision and with the participation of our management, including our chief executive officer and our chief financial officer. Based on that evaluation, these officers have concluded that, as of December 31, 2004, our disclosure controls and procedures were effective to ensure that material information relating to us required to be included in our reports filed under the Exchange Act would be made known to them by others, except as set forth below.

We have voluntarily undertaken to facilitate the filings obligations of our executive officers and directors under Section 16 of the Exchange Act. In December 2004, we experienced a breakdown in communication

that resulting in late Form 4 filings for several of our executive officers after stock option grants were made to them. We have implemented procedures, including altering the administration of the Compensation Committee of our Board of Directors, to provide reasonable assurance that this breakdown in controls will be remedied.

There have been no changes in our internal controls over financial reporting (as defined in Rules 13a-15(b) and 15(d)-15(f) under the Exchange Act) or in other factors that occurred during the period covered by this report that has materially affected or is reasonably likely to materially affect internal controls over financial reporting.

Item 9B. ***Other Information***

The following disclosure would otherwise have been filed on a Current Report on Form 8-K during the first quarter of fiscal year 2005 under the headings "Item 1.01. Entry into a Material Definitive Agreement" and "Item 1.02. Termination of a Material Definitive Agreement":

On March 17, 2005, in response to Douglas Altschuler's request to resign and our agreement to such resignation, we and Mr. Altschuler, our former Senior Vice President, Legal, General Counsel and Secretary, entered into a separation and release agreement pursuant to which Mr. Altschuler's employment by us and his employment agreement terminated, effective March 17, 2005. The terms of the separation and release agreement are generally as follows, subject in all respects to the terms and conditions of the separation and release agreement, which is filed as an exhibit to this Annual Report on Form 10-K and incorporated herein by reference.

Upon effectiveness of the separation and release agreement, Mr. Altschuler is entitled to (1) payment of an amount equal to his current base salary for a period of twelve months and (2) reimbursement of the cost of premiums for our group health plan, until the earlier of twelve months or such coverage otherwise becoming available to Mr. Altschuler. Further, under the separation and release agreement, in addition to his currently vested options, options to acquire an additional 100,000 shares (including approximately 4,200 shares that were acquired after exercise of options, but not sold and are subject to repurchase rights) will vest immediately. All vested options held by Mr. Altschuler will continue to be exercisable in accordance with the terms of our stock option plans, which generally provide that they may be exercised for three months from the date of termination of employment. In consideration of such payments and vesting, Mr. Altschuler is providing a general release of us from all claims and liabilities. Mr. Altschuler is also subject to non-solicitation, cooperation and ongoing confidentiality covenants.

The accelerated vesting of the options concurrent with the termination of employment will result in our recognizing approximately $2,300,000 of non-cash stock compensation expense in the first quarter of 2005. We will also record an expense of approximately $300,000 in other compensation and benefits in the first quarter of 2005 in connection with this termination of employment.

PART III

Item 10. ***Directors and Executive Officers of the Registrant***

The information required with respect to directors is incorporated herein by reference to the information contained in the definitive proxy statement for our 2005 Annual Meeting of Stockholders (the "Proxy Statement"). The information with respect to our audit committee financial expert is incorporated herein by reference to the information contained in the section captioned "Audit Committee" of the Proxy Statement.

We have adopted a Code of Business Conduct and Ethics for our directors, officers (including our principal executive officer, principal financial officer, principal accounting officer or controller, and persons performing similar functions) and employees. Our Code of Business Conduct and Ethics is available in the Corporate Governance section of the Investor Relations section of our website at *www.eyetech.com*. We intend to disclose any amendments to, or waivers from, our Code of Business Conduct and Ethics on our website. Stockholders may request a free copy of the Code of Business Conduct and Ethics by writing to us at Eyetech Pharmaceuticals, Inc., 3 Times Square, New York, New York 10036, Attention: Investor Relations.

Information about compliance with Section 16(a) of the Exchange Act appears under "Section 16(a) Beneficial Ownership Reporting Compliance" in the Proxy Statement. That portion of the Proxy Statement is incorporated by reference into this report.

EXECUTIVE OFFICERS AND OTHER SIGNIFICANT EMPLOYEES

Our executive officers and other significant employees and their respective ages as of March 1, 2005 are as follows:

Name	Age	Position
Executive Officers		
David R. Guyer, M.D.	45	Chief Executive Officer and Director
Paul G. Chaney	47	Chief Operating Officer
Glenn P. Sblendorio	49	Chief Financial Officer and Senior Vice President, Finance
Anthony P. Adamis, M.D.	46	Chief Scientific Officer and Executive Vice President, Research and Development
Other Significant Employees		
Denis O'Shaughnessy, Ph.D.	54	Senior Vice President, Clinical Development

David R. Guyer, M.D. is a co-founder of our company and has been our Chief Executive Officer and a director since February 2000. Dr. Guyer is also currently a voluntary Clinical Professor of Ophthalmology at the New York University School of Medicine. From June 2000 to October 2002, he was also Professor and Chairman of the Department of Ophthalmology at the New York University School of Medicine. Dr. Guyer was Clinical Associate Professor of Ophthalmology at Cornell University Medical Center from July 1995 until June 2000, during which time he also served as Director of Residency Training at Manhattan Eye, Ear & Throat Hospital and was in private practice. Dr. Guyer has also served as the chief medical editor of Ophthalmology Times from July 1996 to the present. From 1992 to 2000, Dr. Guyer was the Study Co-chairman of the Pharmacological Therapy for Macular Degeneration Study Group, a 45-center worldwide group of retinal specialists studying drug therapy for AMD. Dr. Guyer received his M.D. from The Johns Hopkins University School of Medicine and his undergraduate degree from Yale College. He was an ophthalmology resident at The Wilmer Eye Institute, The Johns Hopkins University School of Medicine and completed his fellowship training in retinal surgery at the Massachusetts Eye and Ear Infirmary, a teaching affiliate of Harvard Medical School, where he was a Heed-Knapp Fellow. Dr. Guyer is the author of more than 100 scientific articles concerning ophthalmic diseases.

Paul G. Chaney has been our Chief Operating Officer since August 2003. Mr. Chaney has more than 20 years of experience in the pharmaceutical industry, including from 1996 to August 2003, serving in various

senior management positions at Pharmacia Corporation, a pharmaceutical company acquired by Pfizer in April 2003, where he was responsible for the launch of several ophthalmic products, including Tecnis®, Xalatan and Xalcom®. More specifically, from July 2002 to August 2003, Mr. Chaney served as Vice President, Global Commercial Operations, Ophthalmology Franchise; from May 2001 to June 2002, he served as Vice President, Global Ophthalmology Business; from February 2000 to April 2001, he served as Vice President, Global Pharmaceutical Ophthalmology; from February 1998 to February 2000, he served as Business Director, Ophthalmology, North America; and from February 1996 to February 1998, he served as Director, U.S. Ophthalmology Business. Mr. Chaney received a double B.A. with honors in English and Biological Sciences from the University of Delaware.

Glenn P. Sblendorio has been our Chief Financial Officer and Senior Vice President, Finance since February 2002. From July 2000 to February 2002, Mr. Sblendorio served as Senior Vice President of Business Development for The Medicines Company, a specialty pharmaceutical company. From 1998 to July 2000, Mr. Sblendorio was the Chief Executive Officer, Chief Financial Officer and Managing Director of MPM Capital Advisors, LLC, an investment bank specializing in healthcare related transactions. Mr. Sblendorio's pharmaceutical experience also includes 12 years at Hoffmann-La Roche, Inc., a pharmaceutical company, in a variety of senior financial positions, including Chief Financial Officer of Roche Molecular Systems and Head of Finance-Controller for Amgen/Roche Europe. Mr. Sblendorio received his B.A. in Accounting from Pace University and his M.B.A. in Finance from Fairleigh Dickinson University.

Anthony P. Adamis, M.D. is a co-founder of our company and has been our Chief Scientific Officer and Senior Vice President, Research and Development since July 2002. Dr. Adamis was promoted to Chief Scientific Officer and Executive Vice President, Research and Development in January 2005. Dr. Adamis has served as a member of our Scientific Advisory Board since February 2002 and was our Director of Preclinical Research from April 2000 to June 2002. From January 1998 to June 2002, Dr. Adamis was an Associate Professor of Ophthalmology at Harvard Medical School. From 1992 to June 2002, Dr. Adamis served as Director of Residency Training in Ophthalmology at the Massachusetts Eye and Ear Infirmary, a teaching affiliate of Harvard Medical School. From 2000 to 2002, he also served as a principal investigator and co-director of the Retina Research Institute for Diabetic Retinopathy and Macular Degeneration at the Massachusetts Eye and Ear Infirmary. From January 2001 to December 2001, Dr. Adamis also served as President of the Medical Staff and from January 2001 to December 2001 was a member of the board of directors of the Massachusetts Eye and Ear Infirmary. Dr. Adamis is a specialist in ocular vascular disease and ocular drug delivery. He co-discovered the role that VEGF plays in new blood vessel growth and blood vessel leakage related to various diseases of the eye. Dr. Adamis received his M.D. with Honors from the University of Chicago Pritzker School of Medicine and his undergraduate degree from the University of Illinois, Urbana. Dr. Adamis completed his ophthalmology residency training at the University of Michigan. Dr. Adamis is the author of more than 100 scientific articles concerning ophthalmic diseases.

Denis O'Shaughnessy, Ph.D. has been our Senior Vice President, Clinical Development since August 2000. From November 1990 to July 2000, Dr. O'Shaughnessy held various clinical research and management roles with Hoffmann-La Roche Inc., including Senior Manager responsible for overseeing global clinical research programs. Dr. O'Shaughnessy received his Ph.D. from Royal Post-Graduate Medical School in the United Kingdom and his undergraduate degree from London University.

Item 11. ***Executive Compensation***

Information about compensation of our named executive officers appears under "Executive Compensation" and under "Compensation Committee Interlocks and Insider Participation" in the Proxy Statement. Information about compensation of our directors appears under "Director Compensation Arrangements" and "Stock Ownership of Certain Beneficial Owners and Management" in the Proxy Statement. Those portions of the Proxy Statement are incorporated by reference into this report.

Item 12. ***Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters***

Information about security ownership of certain beneficial owners and management appears under "Stock Ownership of Certain Beneficial Owners and Management" in the Proxy Statement. Information regarding securities authorized for issuance under equity compensation plans appears under "Equity Compensation Plan Information" in the Proxy Statement. Information regarding securities authorized for issuance under equity compensation plans appears under "Equity Compensation Plan Information" in the Proxy Statement. Those portions of the Proxy Statement are incorporated by reference into this report.

Item 13. ***Certain Relationships and Related Transactions***

Information about certain relationships and related transactions appears under "Certain Relationships and Related Transactions" in the Proxy Statement. That portion of the Proxy Statement is incorporated by reference into this report.

Item 14. ***Principal Accountant Fees and Services***

Information about principal accountant fees and services as well as related pre-approval policies appears under "Independent Auditor's Fees" and "Audit Committee Pre-Approval of Audit and Permissible Non-Audit Services of Independent Auditors" in the Proxy Statement. Those portions of the Proxy Statement are incorporated by reference into this report.

PART IV

Item 15. ***Exhibits and Financial Statement Schedules***

(a) Financial Statements and Schedules.

Index to consolidated financial statements appears on page F-1.

(b) Exhibits

Exhibit Number	Description
3.1(1)	Amended and Restated Certificate of Incorporation of the Registrant
3.2(1)	Amended and Restated Bylaws of the Registrant
4.1(3)	Specimen Certificate evidencing shares of common stock
4.2(2)	Warrant Agreement, dated as of March 31, 2000, by and between the Registrant and Gilead Sciences, Inc.
4.3(2)	Warrant Agreement Amendment, dated as of September 4, 2003, by and among the Registrant, Gilead Sciences, Inc. and University License Equity Holdings, Inc.
4.4†(2)	Series D Preferred Stock Purchase Agreement, dated as of December 17, 2002, by and between the Registrant, Pfizer Ireland Pharmaceuticals and Pfizer Inc.
4.5(2)	Amended and Restated Investors' Rights Agreement, dated as of February 7, 2003, by and among the Registrant and the parties listed therein
10.1(2)	2001 Stock Plan, as amended
10.2(1)	2003 Stock Incentive Plan
10.3(1)	2003 Employee Stock Purchase Plan
10.4†(2)	License Agreement, dated as of December 17, 2002, by and between Pfizer Inc. and the Registrant
10.5†(2)	Collaboration Agreement, dated as of December 17, 2002, by and between Pfizer Inc. and the Registrant
10.6†(2)	License, Manufacturing and Supply Agreement, dated February 5, 2002, by and between Shearwater Corporation and the Registrant
10.7†(2)	Licensing Agreement, dated as of March 30, 2000 and amended on May 9, 2000, December 4, 2001 and April 12, 2002, by and between Gilead Sciences, Inc. and the Registrant
10.8†(2)	License Agreement, dated as of December 31, 2001, by and between Isis Pharmaceuticals, Inc. and the Registrant
10.9(2)	Consulting Agreement, dated as of October 30, 2001, by and between the Registrant and Samir Patel
10.10(7)	Amendment No. 1, dated May 4, 2004, to Consulting Agreement by and between the Registrant and Samir Patel.
10.11	Amendment No. 2, dated January 3, 2005, to Consulting Agreement by and between the Registrant and Samir Patel.
10.12	Employment Agreement, dated as of January 4, 2005, by and between the Registrant and Samir Patel.
10.13(2)	Executive Employment Agreement, dated as of April 12, 2000, by and between the Registrant and David R. Guyer
10.14(2)	Amendment to Executive Employment Agreement, dated as of August 25, 2003, by and between the Registrant and David R. Guyer
10.15(2)	Employment Agreement, dated as of August 25, 2003, by and between Paul Chaney and the Registrant
10.16(8)	Amended and Restated Amendment to Employment Agreement, dated as of November 15, 2004, by and between the Registrant and Glenn Sblendorio

Exhibit Number	Description
10.17(8)	Amended and Restated Amendment to Employment Agreement, dated as of August 20, 2004, by and between the Registrant and Anthony P. Adamis
10.18	Amendment to Employment Agreement, dated as of January 3, 2005, by and between the Registrant and Anthony P. Adamis
10.19(2)	Employment Agreement, dated as of August 25, 2003, by and between Douglas H. Altschuler and the Registrant
10.20(10)	Summary description of the 2005 compensation for directors and named executive officers (as defined in the Registrant's Proxy Statement) of the Registrant
10.21(2)	Restricted Stock Purchase Promissory Note, dated July 1, 2002, issued by Anthony P. Adamis to the Registrant
10.22(2)	Stock Pledge Agreement, dated July 1, 2002, by and between Anthony P. Adamis and the Registrant
10.23(2)	Sublease Agreement, dated as of December 19, 2001 and amended as of February 22, 2002, by and between AnswerThink, Inc., successor-in-interest to AnswerThink Consulting Group, Inc., and the Registrant
10.24(2)	Lease Agreement, dated March 14, 2002, by and between First Industrial, L.P. and the Registrant
10.25(2)	Commercial Lease, dated March 27, 2002, by and between Cummings Properties, LLC and the Registrant
10.26(9)	Lease Agreement, dated as of May 13, 2004, by and between ARE-35 Hartwell Avenue, LLC and the Registrant
10.27†(4)	Manufacturing and Supply Agreement, dated as of November 11, 2003, by and between Raylo Chemicals, Inc. and the Registrant
10.28†(5)	Letter of Understanding, effective as of September 1, 2003, by and between the Registrant and Raylo Chemicals, Inc., as amended
10.29†(5)	Manufacturing and Supply Agreement, dated as of November 26, 2003 by and between the Registrant and Gilead Sciences, Inc.
10.30(6)	Sub-Sublease Agreement, dated December 19, 2003, by and between Instinet Global Holdings, Inc. and the Registrant
10.31	Separation and Release Agreement, dated March 18, 2004 between Registrant and Douglas H. Altschuler
21.1	List of Subsidiaries
23.1	Consent of Ernst & Young LLP
31.1	Rule 13a-14(a)/15d-14(a) Certification of Principal Executive Officer
31.2	Rule 13a-14(a)/15d-14(a) Certification of Principal Financial Officer
32.1	Section 1350 Certification of Chief Executive Officer
32.2	Section 1350 Certification of Chief Financial Officer

(1) Incorporated by reference to the Registrant's Annual Report on Form 10-K filed on March 24, 2004

(2) Incorporated by reference to the Registrant's Registration Statement on Form S-1 (SEC File No. 333-108781) filed on September 12, 2003

(3) Incorporated by reference to the Registrant's Registration Statement on Form S-1 (SEC File No. 333-108781) filed on October 21, 2003

(4) Incorporated by reference to the Registrant's Registration Statement on Form S-1 (SEC File No. 333-108781) filed on November 14, 2003

(5) Incorporated by reference to the Registrant's Registration Statement on Form S-1 (SEC File No. 333-108781) filed on December 18, 2003

(6) Incorporated by reference to the Registrant's Registration Statement on Form S-1 (SEC File No. 333-108781) filed on January 27, 2004

(7) Incorporated by reference to the Registrant's Quarterly Report on Form 10-Q filed on May 12, 2004

(8) Incorporated by reference to the Registrant's Quarterly Report on Form 10-Q filed on November 15, 2004

(9) Incorporated by reference to the Registrant's Quarterly Report on Form 10-Q filed on August 13, 2004

(10) Incorporated by reference to the Registrant's Current Report on Form 8-K filed on February 15, 2005

† Confidential treatment granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of New York, New York on the 21st day of March, 2005.

EYETECH PHARMACEUTICALS, INC.

By: /s/ DAVID R. GUYER
David R. Guyer, M.D.
Chief Executive Officer, Director

Pursuant to the requirements of the Securities Act of 1934, as amended, this Annual Report on Form 10-K has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ DAVID R. GUYER, M.D. David R. Guyer, M.D.	Chief Executive Officer, Director (Principal Executive Officer)	March 21, 2005
/s/ GLENN P. SBLENDORIO Glenn P. Sblendorio	Chief Financial Officer (Principal Financial and Accounting Officer)	March 21, 2005
/s/ JOHN P. MCLAUGHLIN John P. McLaughlin	Chairman of the Board of Directors	March 21, 2005
/s/ SRINIVAS AKKARAJU, M.D., PH.D. Srinivas Akkaraju, M.D., Ph.D.	Director	March 21, 2005
/s/ MARTY GLICK Marty Glick	Director	March 21, 2005
/s/ SAMIR PATEL, M.D. Samir Patel, M.D.	Director	March 21, 2005
/s/ MICHAEL J. REGAN Michael J. Regan	Director	March 21, 2005
/s/ PHILLIP M. SATOW Phillip M. Satow	Director	March 21, 2005
/s/ HENRY SIMON Henry Simon	Director	March 21, 2005
/s/ DAMION E. WICKER, M.D. Damion E. Wicker, M.D.	Director	March 21, 2005

EYETECH PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders
Eyetech Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Eyetech Pharmaceuticals, Inc. as of December 31, 2003 and 2004, and the related consolidated statements of operations, stockholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2004. 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 consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and 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 consolidated financial position of Eyetech Pharmaceuticals, Inc. at December 31, 2003 and 2004, and the consolidated results of their operations and their cash flows for each of the three years in the period ended December 31, 2004, in conformity with United States generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

MetroPark, New Jersey
February 11, 2005

EYETECH PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

	December 31, 2003	December 31, 2004
Current assets:		
Cash and cash equivalents	$ 25,013,756	$ 40,779,860
Marketable securities	106,360,073	170,715,315
Collaboration receivable	2,562,000	91,965,888
Prepaid expenses and other current assets	1,301,027	7,868,007
Total current assets	135,236,856	311,329,071
Property and equipment, net	5,867,582	17,817,388
Restricted cash	5,623,865	5,927,360
Other assets	2,751,375	4,385,189
Total assets	$ 149,479,678	$ 339,459,007
Current liabilities:		
Accounts payable and accrued expenses	$ 14,308,103	$ 25,103,180
Deferred license fee revenue, current portion	5,000,000	13,692,958
Capital lease obligations, current portion	618,350	1,459,544
Deferred rent liability, current portion	171,856	1,038,407
Total current liabilities	20,098,309	41,294,089
Deferred license fee revenue, net of current portion	65,416,663	159,705,676
Capital lease obligations, net of current portion	1,038,279	1,254,645
Other liabilities, net of current portion	425,761	6,066,546
Redeemable convertible preferred stock — $.01 par value; 29,093,695 shares authorized; 25,062,278 and no shares issued and outstanding at December 31, 2003 and 2004, respectively, liquidation preference of $252,053,310 as of December 31, 2003	185,506,532	—
Stockholders' (deficit) equity:		
Convertible preferred stock — $.01 par value; 120,000 and none authorized, issued and outstanding at December 31, 2003 and 2004, respectively; liquidation preference of $225,000 as of December 31, 2003	150,000	—
Preferred stock $.01 par value; 5,000,000 shares authorized, none issued and outstanding at December 31, 2003 and 2004	—	—
Common stock — $.01 par value; 60,000,000 and 125,000,000 shares authorized at December 31, 2003 and 2004, respectively; 4,527,736 issued and 4,102,736 outstanding at December 31, 2003; and 42,329,499 issued and 41,904,499 outstanding at December 31, 2004	45,277	423,295
Additional paid-in capital	28,804,713	382,176,673
Loans to stockholders	(430,666)	—
Deferred compensation	(13,956,265)	(11,817,358)
Treasury stock, at cost	(255,000)	(255,000)
Accumulated other comprehensive income	130,831	(572,984)
Accumulated deficit	(137,494,756)	(238,816,575)
Total stockholders' (deficit) equity	(123,005,866)	131,138,050
Total liabilities and stockholders' (deficit) equity	$ 149,479,678	$ 339,459,007

See accompanying notes.

EYETECH PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,		
	2002	2003	2004
Collaboration revenue:			
License fees	$ —	$ 4,583,337	$ 5,722,499
Reimbursement of development costs	—	36,835,829	43,629,406
Total collaboration revenue	—	41,419,166	49,351,904
Operating expenses:			
Research and development	39,663,303	70,931,916	102,738,907
Sales and marketing	—	4,598,588	33,342,575
General and administrative	5,286,707	6,822,949	17,435,387
Total operating expenses	44,950,010	82,353,453	153,516,868
Loss from operations	(44,950,010)	(40,934,287)	(104,164,964)
Interest income	1,808,727	2,171,226	3,810,429
Interest expense	(32,179)	(248,184)	(151,272)
Loss before income taxes	(43,173,462)	(39,011,245)	(100,505,807)
Provision for income taxes	—	(1,688,000)	—
Net loss	(43,173,462)	(40,699,245)	(100,505,807)
Preferred stock accretion	(5,096,282)	(9,160,382)	(816,013)
Net loss attributable to common stockholders	$(48,269,744)	$(49,859,627)	$(101,321,820)
Historical — Basic and diluted net loss attributable to common stockholders per share	$ (13.06)	$ (12.62)	$ (2.70)
Weighted average shares outstanding — historical basic and diluted	3,697,192	3,950,481	37,587,299
Pro forma — Basic and diluted net loss attributable to common stockholders per share (Note 2)		$ (1.77)	$ (2.56)
Pro forma weighted average shares outstanding — basic and diluted (Note 2)		28,094,165	39,651,420

See accompanying notes.

EYETECH PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' (DEFICIT) EQUITY
For the Years Ended December 31, 2002, 2003 and 2004

	Series A Convertible Preferred Stock		Common Stock		Additional	Loans to	Deferred
	Shares	Amount	Shares	Amount	Paid-In Capital	Stockholders	Compensation
Balance at December 31, 2001	120,000	150,000	4,152,000	41,520	5,294,812	(300,000)	(203,000)
Warrants issued in connection with the issuance of Series C-2					3,384,794		
Deferred compensation related to stock options and restricted Stock, net of cancellations					1,334,763		(1,334,763)
Amortization of deferred compensation							238,600
Exercise of stock options			10,000	100	5,900		
Loan to purchase restricted stock					57,000	(102,000)	
Repayment of loan to purchase restricted stock						5,000	
Options granted to nonemployees					1,048,539		
Preferred stock accretion							
Net loss							
Other comprehensive loss:							
Unrealized depreciation on marketable securities							
Comprehensive loss							
Balance at December 31, 2002	120,000	150,000	4,162,000	41,620	11,125,808	(397,000)	(1,299,163)
Deferred compensation related to stock options, net of cancellations					15,001,255		(15,001,255)
Amortization of deferred compensation							2,344,153
Exercise of stock options			365,736	3,657	280,496	(34,416)	
Repayment of loan to purchase restricted stock						750	
Options granted to nonemployees					2,397,154		
Preferred stock accretion							
Net loss							
Other comprehensive loss:							
Unrealized depreciation on marketable securities							
Comprehensive loss							
Balance at December 31, 2003	120,000	$150,000	4,527,736	$ 45,277	$ 28,804,713	$(430,666)	$(13,956,265)
Deferred compensation related to stock options and restricted stock, net of cancellations					4,729,871		(4,729,871)
Comp charge in connection with acceleration					775,132		
Amortization of deferred compensation							6,868,778
Common stock issued pursuant to equity compensation plans			1,651,302	16,513	3,769,701		
Conversion of series A convertible preferred stock	(120,000)	(150,000)	120,000	1,200	148,800		
Conversion of redeemable convertible preferred stock			27,398,762	273,988	189,189,945		
Common stock issued pursuant to cashless exercise of warrants			680,509	6,805	(6,805)		
Common stock issued pursuant to IPO, net of offering costs of $14,154,225			7,951,190	79,512	152,741,050		
Options granted to non-employees					2,024,266		
Repayment of loan by officer						430,666	
Net loss							
Other comprehensive loss:							
Unrealized depreciation on marketable securities							
Comprehensive loss							
Balance at December 31, 2004	—	—	42,329,499	$423,295	$382,176,673	—	$(11,817,358)

	Treasury Stock		Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Deficit
	Shares	Amount			
Balance at December 31, 2001	500,000	(300,000)	354,695	(39,365,385)	(34,327,358)
Warrants issued in connection with the issuance of Series C-2					3,384,794
Deferred compensation related to stock options, net of cancellations					—
Amortization of deferred compensation					238,600
Exercise of stock options					6,000
Loan to purchase restricted stock	(75,000)	45,000			—
Repayment of loan to purchase restricted stock					5,000
Options granted to nonemployees					1,048,539
Preferred stock accretion				(5,096,282)	(5,096,282)
Net loss				(43,173,462)	(43,173,462)
Other comprehensive loss:					
Unrealized depreciation on marketable securities			(121,907)		(121,907)
Comprehensive loss					(43,295,369)
Balance at December 31, 2002	425,000	(255,000)	232,788	(87,635,129)	(78,036,076)
Deferred compensation related to stock options, net of cancellations					—
Amortization of deferred compensation					2,344,153
Exercise of stock options					249,737
Repayment of loan to purchase restricted stock					750
Options granted to nonemployees					2,397,154
Preferred stock accretion				(9,160,382)	(9,160,382)
Net loss				(40,699,245)	(40,699,245)
Other comprehensive loss:					
Unrealized depreciation on marketable securities			(101,957)		(101,957)
Comprehensive loss					(40,801,202)
Balance at December 31, 2003	425,000	$(255,000)	$ 130,831	$(137,494,756)	$(123,005,866)
Deferred compensation related to stock options and restricted stock, net of cancellations					
Compensation charge in connection with acceleration of options					775,132
Amortization of Deferred compensation					6,868,778
Common stock issued pursuant to equity compensation plans					3,786,214
Conversion of Series A convertible preferred stock					
Conversion of redeemable convertible preferred stock					189,463,932
Common stock issued pursuant to cashless exercise of warrants					
Common stock issued pursuant to IPO, net of offering costs of $14,154,225					152,820,562
Options granted to non-employees					2,024,266
Preferred stock accretion				(816,012)	(816,012)
Repayment of loan by officer					430,666
Net loss				(100,505,807)	(100,505,807)
Other comprehensive loss:					
Unrealized depreciation on marketable securities			(703,815)		(703,815)
Comprehensive loss					(101,209,622)
Balance at December 31, 2004	425,000	$(255,000)	$(572,984)	$(238,816,575)	$ 131,138,050

See accompanying notes.

EYETECH PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended December 31,		
	2002	2003	2004
Operating activities			
Net loss	$(43,173,462)	$(40,699,245)	$ (100,505,807)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	316,728	891,177	2,195,911
Loss on disposal of assets	—	31,268	141,765
Noncash stock-based compensation	1,287,134	4,741,307	9,668,176
Loss on lease termination	—	—	2,475,070
Gain on sale of marketable securities	(333,235)	(16,077)	28,470
Changes in operating assets and liabilities:			
Collaboration receivable	—	(2,562,000)	(89,403,888)
Prepaid expenses and other current assets	(43,073)	77,643	(6,088,997)
Other assets	—	(260,757)	(3,335,037)
Accounts payable and accrued expenses	1,626,614	6,865,625	11,296,041
Deferred license fee revenue	—	70,416,663	102,981,971
Other liabilities	498,212	(44,859)	4,032,265
Net cash provided by (used in) operating activities	(39,821,082)	39,440,745	(66,514,060)
Investing activities			
Purchases of property and equipment	(582,330)	(3,778,026)	(12,532,316)
Purchase of marketable securities	(136,447,734)	(400,556,838)	(3,382,237,258)
Proceeds from sale of marketable securities	126,796,094	357,470,013	3,317,149,730
Increase in restricted cash	(1,084,543)	(2,958,225)	(303,495)
Repayment of loan to stockholders	255,000	750	430,666
Increase in prepaid expenses and other current assets	(39,538)	(407,663)	(477,983)
Increase in other assets	(839,395)	(1,701,223)	—
Net cash (used in) investing activities	(11,942,446)	(51,931,212)	(77,970,655)
Financing activities			
Proceeds from issuance of common stock	6,000	249,737	154,521,783
Proceeds from exercise of stock options	—	—	3,786,214
Proceeds from issuance of redeemable convertible preferred stock and warrants, net	54,154,200	32,022,769	2,640,427
Repayment of capital lease obligations	(127,184)	(560,128)	(697,605)
Net cash provided by financing activities	54,033,016	31,712,378	160,250,818
Net increase in cash and cash equivalents	2,269,488	19,221,911	15,766,104
Cash and cash equivalents at beginning of period	3,522,357	5,791,845	25,013,756
Cash and cash equivalents at end of period	$ 5,791,845	$ 25,013,756	$ 40,779,860
Noncash financing and investing activities			
Fixed assets capitalized using capital leases	$ 2,355,686	$ —	$ 1,755,166
Loans to stockholders in connection with exercise of stock options and stock purchase	$ 102,000	$ 34,416	$ —
Supplemental disclosures of cash flow information			
Cash paid during the period for:			
Interest	$ 32,179	$ 248,184	$ 151,272
Income taxes paid	$ —	$ 1,709,890	$ —

See accompanying notes.

1. Organization and Description of Business

Eyetech Pharmaceuticals, Inc. and its wholly owned subsidiaries (collectively, "Eyetech" or the "Company"), is a biopharmaceutical company that specializes in the development and commercialization of novel therapeutics to treat diseases of the eye. The Company's initial focus is on diseases affecting the back of the eye, particularly the retina. In December 2004, the Company received approval from the FDA to market its first product, Macugen® (pegaptanib sodium injection), for the treatment of neovascular (wet) age-related macular degeneration, known as neovascular AMD, in the United States. The Company began selling Macugen in the United States in January 2005. Macugen is being sold to a limited number of specialty distributors who in turn sell Macugen to physicians, physician group practices, hospitals, federal government buying groups and clinics. The Company is also further developing Macugen for the treatment of neovascular AMD and developing Macugen for the treatment of diabetic macular edema, known as DME, which is a complication of diabetic retinopathy, and retinal vein occlusion, known as RVO, and other agreed upon ophthalmic indications.

The Company formed a wholly owned subsidiary in Ireland in 2002. There has been no activity in this company since inception in 2002. In November 2004, concurrent with the acquisition of a potential second-source manufacturing facility for Macugen, the Company established a wholly owned subsidiary to hold these assets. Revenues and expenses from this acquisition were not material to the Company's results at December 31, 2004. The Company operates in a single business segment.

On February 4, 2004, the Company successfully completed an initial public offering (IPO) of its common stock. The IPO consisted of the sale of 6,500,000 shares of common stock at a price of $21.00 per share. As part of the offering, the Company granted to the underwriters an option to purchase an additional 975,000 shares within 30 days of the IPO to cover over-allotments. This option was exercised in tandem with the IPO. In addition, 476,190 shares of common stock were purchased concurrently with the IPO by Pfizer for $10,000,000 as part of its commitment under Pfizer's collaboration with the Company. (Note 11)

Net proceeds from the IPO, including the sale of stock to Pfizer, after deducting underwriter's discounts and commission and offering expenses were $152,821,000. An additional $2,600,000 was received for the issuance of 469,360 shares of preferred stock in connection with the exercise of preferred stock warrants. An additional 1,867,124 shares of preferred stock were issued on a cashless basis to the holders of 2,728,661 preferred stock warrants, who surrendered 861,567 preferred stock warrants as payment for those shares. All outstanding shares of preferred stock, including those shares issued in connection with warrant exercises, automatically converted to common shares upon the completion of the IPO.

2. Basis of Presentation and Significant Accounting Policies

Consolidation

The accompanying consolidated financial statements include the accounts of Eyetech Pharmaceuticals, Inc. and its wholly owned subsidiaries. All material intercompany account balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with U.S. generally accepted accounting principles 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.

Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less to be cash equivalents. At December 31, 2004 the Company has substantially all of its cash and cash equivalents deposited with one financial institution.

Marketable Securities

Marketable securities are classified as "available-for-sale" and are carried at market value with unrealized gains and losses reported as other comprehensive income or loss, which is a separate component of stockholders'(deficit) equity.

Restricted Cash

Restricted cash of $5,927,000 at December 31, 2004 collateralizes $5,927,000 of outstanding letters of credit associated with the leases of the Company's office and laboratory facilities. The funds are invested in certificates of deposit (Note 13).

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash equivalents and marketable securities. The Company has established guidelines relating to diversification and maturities that allows the Company to manage risk.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, which include cash and cash equivalents, accounts payable and accrued expenses, approximate their fair values. The estimated fair value of the redeemable convertible preferred stock at December 31, 2003 was $526,000,000, based on the IPO common stock value of $21.00 per share. At December 31, 2004, the redeemable convertible preferred stock has been converted to common stock.

Inventory

At December 31, 2004, the Company has not capitalized any inventory as all costs associated with Macugen's active pharmaceutical ingredient and work in process were expensed as research and development costs prior to the approval by the FDA of Macugen on December 17, 2004. There were no finished goods as of December 31, 2004.

Property and Equipment

Property and equipment is stated at cost. Depreciation is computed using the straight-line method over the estimated useful lives of the assets which range from three to seven years. Leasehold improvements are amortized over the estimated useful lives of the assets or related lease terms, whichever is shorter.

Impairment of Long-Lived Asset

The Company assesses impairment of long-lived assets in accordance with Statement of Financial Accounting Standards No. 144, "Accounting for the Impairment or Disposal of Long-Lived Assets" ("SFAS No. 144"). Assessments of the recoverability of long-lived assets are conducted when events or changes in circumstances occur that indicate that the carrying value of the asset may not be recoverable. The assessment of possible impairment is based upon the ability to recover the asset from the expected future

undiscounted cash flows of related operations. No events have been identified that caused an evaluation of the recoverability of the long-lived assets for the years ended December 31, 2002, 2003 and 2004.

Revenue Recognition

Revenues associated with the Company's collaboration with Pfizer consist of non-refundable, up-front license fees and reimbursement of development expenses.

The Company uses revenue recognition criteria outlined in Staff Accounting Bulletin No. 104, "Revenue Recognition in Financial Statements" and Emerging Issues Task Force ("EITF") Issue 00-21, "Revenue Arrangements with Multiple Deliverables" ("EITF 00-21"). Accordingly, revenues from licensing agreements are recognized based on the performance requirements of the agreement. Non-refundable up-front license fees, where the Company has an ongoing involvement or performance obligation, are generally recorded as deferred revenue in the balance sheet and amortized into license fees in the statement of operations over the term of the performance obligation. The Company also receives non-refundable license payments based on the achievement of certain regulatory and sales events. The Company records deferred license revenue when all contractual obligations related to a non-refundable payment have been satisfied and amortizes the payments into license fees in the statement of operations over the remaining term of the related performance obligation.

Revenues derived from reimbursements of costs associated with the development of Macugen are recorded in compliance with EITF Issue 99-19, "Reporting Revenue Gross as a Principal Versus Net as an Agent" ("EITF 99-19"), and EITF Issue 01-14, "Income Statement Characterization of Reimbursements Received For "Out-of-Pocket" Expenses Incurred" ("EITF 01-14"). According to the criteria established by these EITF Issues, in transactions where the Company acts as a principal, with discretion to choose suppliers, bears credit risk and performs part of the services required in the transaction, the Company has met the criteria to record revenue for the gross amount of the reimbursements.

Research and Development Costs

Research and development costs are expensed as incurred.

Stock-Based Compensation

In December 2002, SFAS No. 148, "Accounting for Stock-Based Compensation — Transition and Disclosure — an amendment of FASB Statement No. 123" ("SFAS No. 148") was issued. SFAS No. 148 provides alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation from the intrinsic value-based method of accounting prescribed by APB Opinion No. 25, "Accounting for Stock Issued to Employees" ("APB No. 25"). In addition, SFAS No. 148 amends the disclosure requirements of SFAS No. 123, "Accounting for Stock-Based Compensation" ("SFAS No. 123"). The Company adopted the disclosure requirements of SFAS No. 148 effective December 31, 2002. As allowed by SFAS No. 123, the Company has elected to continue to apply the intrinsic value-based method of accounting prescribed in APB No. 25 and, accordingly, does not recognize compensation expense for stock option grants made at an exercise price equal to or in excess of the fair market value of the stock at the date of grant.

Had compensation cost for the Company's outstanding employee stock options been determined based on the fair value at the grant dates for those options consistent with SFAS No. 123, the Company's net loss and basic and diluted net loss per share, would have been changed to the following pro forma amounts:

	Year Ended December 31,		
	2002	2003	2004
Net loss attributable to common stockholders, as reported..	$(48,269,744)	$(49,859,627)	$(101,321,820)
Add: Non-cash employee compensation as reported	238,600	2,344,153	6,868,778
Deduct: Total stock-based employee compensation expense determined under fair value based method for all awards	(350,877)	(2,450,510)	(11,973,703)
SFAS No. 123 pro forma net loss	$(48,382,021)	$(49,965,984)	$(106,426,745)
Basic and diluted loss attributable to common stockholders per share, as reported	$ (13.06)	$ (12.62)	$ (2.70)
Basic and diluted loss attributable to common stockholders per share, SFAS No. 123 pro forma	$ (13.09)	$ (12.65)	$ (2.83)
Unaudited pro forma basic and diluted net loss attributable to common stockholders per share, SFAS No. 123 pro forma		$ (1.78)	$ (2.68)

SFAS No. 123 pro forma information regarding net loss is required by SFAS No. 123, and has been determined as if the Company had accounted for its stock-based employee compensation under the fair value method prescribed in SFAS No. 123. For periods prior to our IPO on February 4, 2004, the fair value of the options was estimated at the date of grant using the minimum value pricing model. Subsequent to that date the Company began using the Black-Scholes option pricing model. The following assumptions have been used to compute fair market value under each model:

	Year Ended December 31,		
	2002	2003	2004
Volatility.....	—	—	72%
Risk-free interest rate	3.5% - 5.0%	2.8% - 4.2%	3.9% - 4.75%
Dividend yield	0%	0%	0%
Expected life	7 years	5 years	5 years

The effects of applying SFAS 123 in this pro forma disclosure are not indicative of future amounts. Pro forma compensation related to stock option grants is expensed over their respective vesting periods.

The Company accounts for options issued to non-employees under SFAS 123 and EITF Issue 96-18, "Accounting for Equity Investments that are Issued to Other than Employees for Acquiring or in Conjunction with Selling Goods or Services" ("EITF 96-18"). As such, the value of such unvested options is periodically re-measured and income or expense is recognized during their vesting terms.

Comprehensive Loss

The Company reports comprehensive loss in accordance with SFAS No. 130, "Reporting Comprehensive Income" ("SFAS No. 130"). SFAS 130 establishes rules for the reporting and display of comprehensive loss and its components. SFAS No. 130 requires unrealized gains on available-for-sale securities to be included in other comprehensive loss.

Income Taxes

The Company utilizes the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax basis of assets and liabilities and are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

Net Loss Per Share

The Company computes net loss per share in accordance with Statement of Financial Accounting Standards No. 128, "Earnings per Share" ("SFAS No. 128"). Under the provisions of SFAS No. 128, basic net loss per common share ("Basic EPS") is computed by dividing net loss by the weighted-average number of common shares outstanding, excluding shares of common stock which are subject to repurchase and are not vested. Diluted net loss per common share ("Diluted EPS") is computed by dividing net loss by the weighted-average number of common shares, excluding shares of common stock which are subject to repurchase and are not vested 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 the conversion of preferred stock upon the exercise of warrants. Diluted EPS is identical to Basic EPS since common equivalent shares are excluded from the calculation, as their effect is anti-dilutive.

Pro Forma Information (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 automatic conversion of all outstanding convertible preferred stock into shares of the Company's common stock effective upon the closing of the Company's IPO, as if such conversion had occurred at the date of the original issuance. Accordingly, pro forma basic and diluted net loss per common share has been calculated assuming the preferred stock was converted as of the original date of issuance of the preferred stock. Pro forma weighted average shares of 28,094,165 and 39,651,420 is based on the weighted average conversion of 24,143,684 and 2,064,121 shares of our convertible preferred stock for the year ended December 31, 2003 and 2004, respectively.

Reclassification

Certain prior period amounts have been reclassified to conform to current year presentation.

Recently Issued Accounting Pronouncements

On December 16, 2004, the Financial Accounting Standards Board ("FASB") issued SFAS No. 123 (revised 2004), "Share-Based Payment" ("SFAS No. 123(R)"), which is a revision of FASB Statement No. 123 ("SFAS No. 123"), "Accounting for Stock-Based Compensation". SFAS No. 123(R) supersedes APB Opinion No. 25, "Accounting for Stock Issued to Employees" ("APB No. 25"), and amends SFAS No. 95, "Statement of Cash Flows" ("SFAS No. 95"). Generally, the approach in SFAS No. 123(R) is similar to the approach described in SFAS No. 123. However, SFAS No. 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values. Pro forma disclosure will no longer be allowable.

SFAS No. 123(R) must be adopted no later than July 1, 2005. Early adoption will be permitted in periods in which financial statements have not yet been issued. The Company expects to adopt SFAS No. 123(R) on July 1, 2005.

The Company will adopt the "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS No. 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS No. 123 for all awards granted to employees prior to the effective date of SFAS No. 123(R) that remain unvested on the effective date.

As permitted by SFAS No. 123, the Company currently accounts for share-based payments to employees using APB No. 25's intrinsic value method and, as such, generally recognizes no compensation cost for employee stock options. Accordingly, the adoption of SFAS No. 123(R)'s fair value method will have a significant impact on the Company's results of operations, although it will have no impact on the Company's overall financial position. The impact of adoption of SFAS No. 123(R) cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had the Company adopted SFAS No. 123(R) in prior periods, the impact of that standard would have approximated the impact of SFAS No. 123 as described in the disclosure of pro forma net income and earnings per share in Note 2 to the Company's consolidated financial statements.

3. Available for Sale Investments

Available for sale investments consist primarily of federal agency notes, asset backed securities, mortgage backed securities, corporate debt, United States treasury notes and municipal bonds. The following is a summary of available for sale investments as of December 31, 2003 and 2004:

	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
December 31, 2003				
Maturities within one year:				
Corporate notes	$ 24,386,443	$ 9,725	$ (7,720)	$ 24,388,448
Federal agency notes	23,951,489	10,670	(1,695)	23,960,464
Asset-backed securities	32,023,764	100,669	(2,463)	32,121,970
	80,361,696	121,064	(11,878)	80,470,882
Maturities between one to two years:				
Corporate notes	16,316,113	12,833	(3,658)	16,325,288
Federal agency notes	6,909,507	1,031	(14,664)	6,895,874
Mortgage-backed securities	730,202	8,486	—	738,688
Municipal bonds	1,911,724	17,617	—	1,929,341
	25,867,546	39,967	(18,322)	25,889,191
Total	$106,229,242	$161,031	$(30,200)	$106,360,073

	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
December 31, 2004				
Maturities within one year:				
Corporate notes	$ 42,226,280	$ 4,417	$ (85,206)	$ 40,717,367
Federal agency notes	10,181,803	2,851	(16,566)	10,025,965
	52,408,083	7,268	(101,773)	50,743,332
Maturities between one to two years:				
Corporate notes	45,891,785	6,714	(197,840)	45,370,563
Federal agency notes	9,140,212	987	(93,782)	8,980,323
Mortgage-backed securities	3,479,739	—	(17,991)	3,404,501
Asset-backed securities	52,746,356	6,448	(129,770)	52,032,551
Municipal bonds	3,309,543	10,870	—	3,248,732
U.S. Treasury Notes	6,997,773	—	(62,845)	6,935,313
	121,565,408	25,019	(502,227)	119,971,983
Total	$173,973,491	$ 32,287	$(604,000)	$170,715,315

4. Property and Equipment

Property and equipment consists of the following:

	December 31,	
	2003	2004
Furniture and office equipment	$ 562,826	$ 965,028
Computer equipment	1,728,918	3,626,825
Laboratory equipment	4,348,071	7,082,596
Manufacturing equipment	—	5,115,637
Leasehold improvements	559,108	4,554,554
	7,198,923	21,344,640
Accumulated depreciation and amortization	(1,331,341)	(3,527,252)
	$ 5,867,582	$17,817,388

Included in property and equipment are assets recorded under capital leases with a cost of approximately $2,355,686 and $4,110,852 at December 31, 2003 and 2004, respectively. Amortization of the assets recorded under capital leases is included with depreciation expense. The accumulated amortization related to these assets under capital leases was approximately $649,000 and $1,149,000 at December 31, 2003 and 2004, respectively.

5. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	December 31, 2003	December 31, 2004
Milestones	$ —	$ 6,000,000
Clinical development expenses	3,862,646	3,725,479
Manufacturing expenses	2,469,740	2,597,638
Payroll and related expenses	2,483,688	6,272,244
Professional fees	1,876,267	1,516,321
Collaboration payable	715,000	2,142,000
Other expenses	2,900,762	2,849,499
	$14,308,103	$25,103,180

6. Redeemable Convertible Preferred Stock and Stockholders' (Deficit) Equity

Common Stock

As of December 31, 2004, the Company is authorized to issue 125,000,000 shares of common stock and 5,000,000 shares of preferred stock issuable in one or more series to be designated by the Company's Board of Directors. Each holder of common stock is entitled to one vote for each share of common stock held of record on all matters on which stockholders generally are entitled to vote.

The Company had reserved shares of common stock for issuance as follows:

	December 31, 2003	December 31, 2004
Common stock options and restricted stock grants	9,049,250	7,688,783
Conversion of Series A preferred stock	120,000	—
Conversion of Series B preferred stock	5,790,331	—
Conversion of Series C-1 and C-2 preferred stock	16,524,694	—
Conversion of Series D preferred stock	2,747,253	—
Exercise of warrants to purchase Series B, C-1 and C-2 preferred stock	4,031,414	—
	38,262,942	7,688,783

Convertible Preferred Stock

The following table provides details of the issuance of preferred stock by the Company:

Preferred Issue	Issue Date	Shares	Proceeds	Converted at IPO to Common	Outstanding at 12/31/04
Series A	March 2000	120,000	$ 150,000	120,000	—
Series B	April 2000	5,766,332	$ 34,473,000	5,766,332	—
Series B	January 2001	20,666	$ 124,000	20,666	—
Series C-1	July 2001	7,964,229	$ 53,461,000	7,964,229	—
Series C-2	August 2001	7,521,777	$ 54,157,000	7,521,777	—
Series D	December 2002	2,747,253	$ 24,737,000	2,747,253	—
Totals		24,140,257	$167,102,000	24,140,257	—

Concurrent with the closing of the Company's IPO in February 2004, all outstanding shares of preferred stock were converted on a one to one basis into common stock.

Preferred Stock Warrants

The following table provides details of the issuance of warrants in connection with the sale of preferred stock by the Company:

Preferred Stock Series	Issue Date	Warrants	Exercise Price	Fair Value at Issuance	Cash Exercise	Cashless Exercise	Warrants Surrendered in Cashless Exercise	Outstanding at 12/31/04
Series B	March 2000	1,142,902	$6.00	$1,040,000	149,566	709,517	283,819	—
Series C-1	July 2001	1,592,846	$6.80	$2,134,000	688,134	611,746	292,966	—
Series C-2	August 2001	1,504,354	$7.20	$3,385,000	673,681	545,861	284,812	—
Total		4,240,102		$6,559,000	1,511,381	1,867,124	861,597	—

Proceeds from the exercises of warrants aggregated $7,286,000 and $2,640,000 through December 31, 2003 and 2004, respectively. In addition, other warrant holders exercised warrants, utilizing the cashless exercise provisions of the warrant agreements, to purchase 1,867,124 by exchanging 861,597 warrants at the IPO price of $21.00 per share. At completion of the IPO, 833,333 warrants to purchase Series B redeemable convertible preferred stock automatically converted into warrants to purchase 833,333 shares of common stock. These warrants were exercised through the surrender of 152,824 warrants at an average market price of $26.72. No warrants remain outstanding at December 31, 2004.

Voting

Preferred stockholders were entitled to the number of votes equal to the number of shares of common stock into which each share of preferred stock was convertible.

Dividends

The holders of Series A, Series B, Series C-1, Series C-2 and Series D were entitled to annual non-cumulative dividends when, and if, declared, prior and in preference to any dividends payable on common stock, at a rates from $0.10 per share to $0.73 per share. In connection with the conversion of preferred stock into common stock upon the completion of the IPO, all dividend rights ceased.

Liquidation

In the event of a defined liquidation event ("Liquidation Event"), that results in the transfer of 50% or more of the outstanding voting power of the Company or a sale of substantially all the assets of the Company, preferred stockholders were entitled to, prior and in preference to any other stockholders, a liquidation preference distribution of the sum of 1.5 times the original per share purchase price paid to the Company, plus all declared and unpaid dividends. The Series B, Series C-1, Series C-2 and Series D preferred stockholders rank senior in preference to the Series A preferred stockholders. After payment of full preferential amounts to preferred stockholders, the remaining assets shall be distributed ratably among the holders of common stock.

The following table summarizes convertible preferred stock issued and outstanding (excluding preferred stock warrants of 4,031,414), with liquidation preferences for each series at December 31, 2003:

	Authorized Shares	Issued and Outstanding	Liquidation Preference
Series A	120,000	120,000	$ 225,000
Series B	7,763,233	5,790,331	52,112,979
Series C-1	9,557,077	8,496,054	86,659,751
Series C-2	9,026,132	8,028,640	86,709,312
Series D	2,747,253	2,747,253	37,500,003
	29,213,695	25,182,278	$263,207,045

In connection with the conversion of preferred stock into common stock upon the completion of the IPO, all liquidation rights ceased.

Conversion

Each holder of preferred stock had the ability to convert at any time, at its option, shares of preferred into common stock on a one-for-one basis subject to certain adjustments. All series of preferred stock were converted into common shares at the completion of the IPO.

Redemption

At any time on or after July 20, 2010, the Company shall redeem for cash convertible preferred stock at the greater of the sum of 1.5 times the original series issue price plus declared but unpaid dividends or the amount per share as would have been payable had each share been converted into common stock. Accordingly, through the closing date of the Company's IPO, the Company recorded and accreted the Series B, Series C-1, Series C-2 and Series D to its defined redemption value. In connection with the conversion of preferred stock to common upon completion of the IPO, all redemption rights ceased.

7. Stock Options

The Company maintains several equity compensation plans and has reserved a maximum of 4,400,000 shares under the Company's 2003 Stock Incentive Plan (the "2003 Incentive Plan"), 500,000 shares under the Company's 2003 Employee Stock Purchase Plan (the "2003 Purchase Plan"), 8,175,000 shares under the Company's 2001 Stock Option Plan (the "2001 Plan") and 2,747,500 shares for stock options granted prior to the adoption of the 2001 Plan. Stock options and restricted stock awards may be granted to employees and consultants. Beginning in 2005, the 2003 Incentive Plan, is subject to annual increases in accordance with the terms of the 2003 Incentive Plan. Upon effectiveness of the 2003 Incentive

Plan at completion of the Company's IPO, the Company stopped granting stock options or other awards under the Company's 2001 Plan.

Granted stock options generally vest over a four-year period with substantially all options vesting with respect to 25% of the shares on the first anniversary of the grant date and thereafter in thirty-six monthly installments and restricted stock awards typically vest 25% per year over a four year period. Options expire ten years from date of grant. Additionally, under the terms of the 2001 Plan, granted options may be exercised immediately into restricted shares. Options that are exercised into restricted shares of common stock continue to vest under the original terms of the related options. Under the terms of the Plan, should the employee terminate employment with the Company, the Company may repurchase those shares that are unvested at the termination date at the original purchase price.

The following table summarizes option activity for the Company:

	Common Stock Options	Weighted-Average Exercise Price
Outstanding at January 1, 2002	1,983,500	$ 1.24
Granted	1,885,000	1.38
Exercised	(10,000)	0.60
Cancelled	(105,084)	0.89
Outstanding at December 31, 2002	3,753,416	$ 0.98
Granted	1,518,500	5.18
Exercised	(365,736)	0.78
Cancelled	(209,264)	2.33
Outstanding at December 31, 2003	4,696,916	$ 2.30
Granted	2,683,919	34.97
Exercised	(1,547,711)	1.99
Cancelled	(450,495)	8.58
Outstanding at December 31, 2004	5,382,629	$18.16

The following table summarizes information about vested stock options outstanding:

	December 31,		
	2002	2003	2004
Vested stock options	1,210,891	1,844,793	1,490,855
Weighted average exercise price	$ 0.60	$ 0.87	$ 3.17

The following table summarizes information about stock options outstanding at December 31, 2004:

	Stock Options Outstanding			Stock Options Outstanding and Exercisable	
Range of Exercise Prices	Shares	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Shares	Weighted Average Exercise Price
$ 0.60 to $ 1.40	1,437,234	6.71	$ 1.01	1,437,234	$ 1.01
$ 1.41 to $10.00	1,443,706	8.42	4.48	1,443,706	4.48
$10.01 to $30.00	1,018,927	9.11	28.63	117,926	18.15
$30.01 to $47.95	1,482,762	9.67	40.90	—	
Total	5,382,629	8.44	$18.16	2,998,866	$ 3.39

In connection with the granting of employee stock options and restricted stock awards in 2002, 2003 and 2004, the Company recorded deferred compensation, net of forfeitures and cancellations of approximately $1,335,000, $15,001,000 and $4,730,000, respectively. Deferred compensation is being amortized over the vesting period of the grants resulting in non-cash stock-based compensation expense of approximately $239,000, $2,344,000 and $6,869,000 for the years ended December 31, 2002, 2003 and 2004, respectively. Included in the calculation of deferred compensation and compensation expense for 2004 were 121,626 shares of restricted stock that the Company granted to employees only.

For the years ended December 31, 2002, 2003, and 2004, the Company granted a total of 137,500, 5,000 and 22,500 respectively, in stock options to certain consultants and Scientific Advisory Board members. The Company has accounted for these options in accordance with EITF 96-18 and, accordingly, recorded non-cash expense of $1,049,000, $2,397,000 and $2,024,000 for the years ended December 31, 2002, 2003, and 2004, respectively. The Company will continue to re-measure the fair value of unvested stock options to these consultants and Scientific Advisory Board members until vesting is complete.

On September 10, 2003, the Company's Board of Directors approved the Company's 2003 Stock Incentive Plan (the "2003 Incentive Plan"). The 2003 Incentive Plan, which was approved by stockholders in December 2003, became effective on February 4, 2004, the date that the registration statement relating to the Company's IPO was declared effective.

On September 10, 2003, the Company's Board of Directors approved the Company's 2003 Employee Stock Purchase Plan (the "2003 Purchase Plan"). The 2003 Purchase Plan, which was approved by stockholders in December 2003, became effective on February 4, 2004, the date that the registration statement relating to the Company's IPO was declared effective. Under the 2003 Purchase Plan, 500,000 shares of common stock are reserved for sale to participating employees at an amount equal to 85% of the lower of the closing price of our common stock on the first day or the last day of the offering period. During the year ended December 31, 2004, 39,715 shares were issued to employees at a price of $17.85, resulting in proceeds of $709,000. The 2003 Purchase Plan qualifies under the requirements of Section 423 of the Internal Revenue Code as a non-compensatory plan and is therefore considered under APB 25 to be non-compensatory. As a result, the Company did not record any expense in connection with the 2003 Purchase Plan during the year ended December 31, 2004.

8. Loss Per Share

The following table sets forth the computation of basic and diluted net loss attributable to common stockholders per share.

	Year Ended December 31,		
	2002	2003	2004
Numerator:			
Net loss	$(43,173,462)	$(40,699,245)	$(100,505,807)
Preferred stock accretion	(5,096,282)	(9,160,382)	(816,013)
Numerator for basic and diluted net loss attributable to common stockholders per share — net loss attributable to common stockholders	$(48,269,744)	$(49,859,627)	$(101,321,820)
Denominator:			
Denominator for basic and diluted net loss attributable to common stockholders per share — weighted average shares	3,697,192	3,950,481	37,587,299
Basic and diluted net loss attributable to common stockholders per share	$ (13.06)	$ (12.62)	$ (2.70)
Denominator for unaudited pro forma basic and diluted net loss attributable to common stockholders per share — weighted average shares (Note 2)		28,094,165	39,651,420
Unaudited pro forma basic and diluted net loss attributable to common stockholders per share (Note 2)		$ (1.77)	$ (2.56)

The following table shows dilutive common share equivalents outstanding, which are not included in the above historical calculations, as the effect of their inclusion is anti-dilutive during each period:

	Year Ended December 31,		
	2002	2003	2004
Preferred stock	21,393,004	25,182,278	—
Options	3,753,416	4,696,916	5,382,629
Warrants	5,073,435	4,031,414	—
	30,219,855	33,910,608	5,382,629

9. Income Taxes

At December 31, 2004, the Company has a net operating loss for federal income tax purposes of approximately $174,804,000, of which $24 million is attributable to stock option exercises, which begins to expire in 2020.

The Company has research and development tax credit carryforwards at December 31, 2004 of approximately $3,458,107, which will begin to expire in 2022. The Company also has alternative minimum tax credit carryforwards at December 31, 2004 of approximately $666,556, which are available for use against the Company's regular tax liability in the future. If an ownership change, as defined under Internal Revenue Code Section 382, occurs, the use of these carry forwards may be subject to limitation.

Provision for income tax at December 31, 2002, 2003 and 2004 consists of:

	2002	2003	2004
Current Federal alternative minimum tax	$ —	$ 833,000	$ —
Current State taxes	—	855,000	—
	$ —	$1,688,000	$ —

Deferred income taxes reflect the net effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The Company's deferred tax assets relate primarily to net operating loss carryforwards and deferred license fee revenue. The change in valuation allowance was approximately $17,703,000 and $51,764,000 for the years ended December 31, 2003 and 2004, respectively. At December 31, 2003 and 2004, a valuation allowance was recorded to fully offset the net deferred tax asset. Significant components of the Company's deferred tax assets are as follows:

	Year Ending December 31,	
	2003	2004
Deferred tax assets:		
Net operating loss carryforwards	$ 17,326,000	$ 69,921,000
Stock-based compensation	2,286,000	—
Start-up costs, net of amortization	122,000	9,000
Deferred license fee revenue	28,167,000	26,167,000
Alternative minimum tax credit	833,000	667,000
Research and development tax credit	1,027,000	3,458,000
Deferred rent liability	197,000	2,813,000
Total gross deferred tax assets	49,958,000	103,035,000
Deferred tax liabilities:		
Depreciation	(993,000)	(2,306,000)
Total gross deferred tax liabilities	(993,000)	(2,306,000)
Valuation allowance	(48,965,000)	(100,729,000)
Net deferred tax assets	$ —	$ —

A reconciliation of the statutory tax rates and the effective tax rates for the years ended December 31, 2002, 2003 and 2004 is as follows:

	Year Ended December 31,		
	2002	2003	2004
Statutory rate	(34)%	(34)%	(34)%
State and local income taxes (net of federal tax benefit)	(6)	(4)	(6)
Tax credits	—	(3)	(2)
Change in valuation allowance	40	45	42
	0%	4%	0%

10. Loans to Stockholders

The Company had made loans to certain current and former executive officers and a consultant in connection with the exercise of stock options and purchases of common stock from the Company. The total outstanding balance of these loans at December 31, 2003 was $430,666 and was collateralized by 633,333 shares of common stock, which were held by the Company. During the year ended December 31, 2004, these loans were repaid in full and the common stock collateral was released by the Company. At December 31, 2004, the Company has no outstanding loans to stockholders.

11. Collaboration Agreements

In March 2000, the Company licensed the rights to certain technology from a corporate licensor in exchange for an up-front license fee of $7,000,000 and a warrant to purchase 833,333 shares of Series B convertible preferred stock at an exercise price of $6.00 per share. The warrant was converted to a warrant to purchase common shares at the close of the Company's IPO and is exercisable at any time through March 30, 2005. During 2004, the warrant was exercised into 680,509 shares of common stock on a cashless basis in exchange for the surrender of 152,824 warrants. During 2004, the Company recognized as research and development expense $8,000,000 in license fees in connection with regulatory filings and will pay an additional $7,000,000 in connection with the commercial launch of Macugen in 2005. In addition, the Company may be required to make additional payments aggregating up to $10,000,000 upon the achievement of future development and commercial launch milestones specified in the licensing agreement.

In December 2001, the Company signed a license agreement for the nonexclusive rights to certain technology from a corporate licensor in exchange for an initial irrevocable and nonrefundable license fee of $2,000,000, which was paid in 2002. During 2004, the Company recorded $1,000,000 in license fees upon filing with the FDA for marketing approval of Macugen. At the time FDA approval of Macugen was received, the Company recorded $3,000,000 in license fees payable on this license agreement and will amortize this amount over the remaining life of the patent on the licensed technology. Additionally, the Company may be required to make additional payments aggregating up to $2,750,000 upon the achievement of specified regulatory milestones with respect to the use of Macugen for other therapeutic indications.

In February 2002, the Company entered into a license, manufacturing and supply agreement for the use of certain technology rights to certain patents of a component of Macugen. The contract calls for specified pricing based on quantities purchased. The Company paid an up-front license fee of $1,500,000 at signing. For the year ended December 31, 2004, the Company recognized $1,500,000 as research and development expense in license fees paid in connection with regulatory filings for Macugen. At December 31, 2004, the Company recorded $3,000,000 due this licensor as prepaid royalty expense which will be credited against future royalties due the licensor in connection with sales of Macugen.

In December 2002, Pfizer and the Company entered into several concurrent agreements to jointly develop and commercialize Macugen. Under the terms of the agreement, which became effective February 3, 2003 when government approval was obtained, Pfizer made initial payments of $100,000,000 which included the purchase of 2,747,253 shares of the Company's Series D preferred stock for $24,736,944, net of issuance costs and a $75,000,000 initial license fee which is being amortized over the expected term of the agreement (estimated at 15 years). In addition, Pfizer agreed to purchase from the Company, up to an additional $25,000,000 of the Company's capital stock at the then current market price upon the completion of certain events, including $10,000,000 of the Company's common stock at the IPO price concurrently with the successful completion of an IPO. Concurrent with the IPO during 2004, Pfizer purchased 476,190 shares of common stock at $21.00 per share and is obligated to purchase the remaining $15,000,000 of common stock in connection with the approval of Macugen. (Note 16)

During 2004, the Company received an additional $15.5 million in license fees based on regulatory filings in the United States and European Union and has recorded a receivable of $90 million in connection with the FDA approval of Macugen. These license fees are being amortized over the remaining expected term of the agreement (estimated at approximately 13 years).

Based on the achievement of certain specified worldwide regulatory submission and approvals, the Company would be eligible to receive up to an additional $90,000,000 in license payments. The Company also has the potential to receive up to an additional $450,000,000 in milestone payments, which are contingent upon successful commercialization of Macugen and which are based on attainment of agreed-upon sales levels. Pfizer may terminate the collaboration relationship upon six to twelve months' prior notice, depending on when such notice is given.

Upon commercial launch in 2005, Macugen will be co-promoted by the Company and Pfizer in the United States where Eyetech will have an ophthalmology sales force, maintain the inventory and book all United States product sales. The Company and Pfizer will share in profits and losses from the sale of Macugen products in the United States. Outside the United States, Pfizer will market the product exclusively under a license, for which the Company will receive royalty income.

Under the terms of the agreement, both parties will expend funds related to the co-promotion and development of Macugen. Pfizer will generally fund a majority of the ongoing development costs incurred pursuant to an agreed upon development plan covering the development of Macugen for AMD, DME, RVO and other agreed upon ophthalmic indications. In certain instances, the Company will reimburse Pfizer for the Company's share of costs that Pfizer incurs.

The following table details the revenues and expenses incurred for research and development and marketing expenses in connection with this agreement:

	Year Ended December 31,	
	2003	2004
License fee amortization	$ 4,583,337	$ 5,722,499
Reimbursement of development expense	$36,835,829	$ 43,629,406
Development and marketing expense	$ 3,305,552	$ 8,224,000
Payments received from Pfizer	$31,683,277	$ 41,329,917
Collaboration Receivable and Payable:		
Collaboration receivable	$ 2,562,000	$ 294,000
Equipment receivable	$ —	$ 1,671,888
Milestone receivable	$ —	$ 90,000,000
Total Receivable	$ 2,562,000	$ 91,965,888
Deferred license fee revenue	$70,416,633	$170,213,235
Deferred collaboration revenue		$ 3,185,399
Collaboration payable	$ 715,000	$ 2,142,000
Total Deferred Revenues and Payable *	$71,131,663	$175,540,634

* Deferred license fee revenues are payments received in connection with up-front license fees and are amortized to license fee revenue over the life of the contract. Deferred collaboration revenues are payments received in advance of the incurrence of collaboration costs and costs related to the reimbursement of certain capital expenditures. Collaboration payable represents the Company's share of costs incurred by Pfizer which the Company is contractually liable to pay to Pfizer.

12. Capital Leases

The Company leases laboratory equipment and other equipment under capital leases that bear interest from 8.6% to 10.1% and expire in 2006. The following is a schedule of the future minimum lease payments under these capital leases as of December 31, 2004:

Year Ending December 31,	
2005	$1,625,844
2006	1,329,057
Total	2,954,901
Less amount representing interest	240,712
Present value of the minimum lease payments	2,714,189
Less current portion of capital lease obligations	1,459,544
	$1,254,645

13. Commitments

The Company leases office and laboratory space in New York, New York, Cedar Knolls, New Jersey and Lexington, Massachusetts. Under existing lease agreements, the Company has secured bank letters of credit totaling approximately $5,927,000, which are fully cash collateralized and the cash is categorized as restricted cash in the balance sheet.

Rent expense for the years ended December 31, 2002, 2003 and December 31, 2004 was approximately $1,380,000, $1,316,000, and $4,806,000, respectively. In connection with the Company's decision to relocate its corporate headquarters in New York, New York and its research laboratories in Woburn, Massachusetts, the Company recognized a loss of $2,475,000. The loss is based on the present value of the cash flows associated with the current leases. The Company used a risk adjusted interest rate of 7.5% to discount the cash flows and assigned probabilities to various sub-lease scenarios to arrive at a weighted average probability of loss as required by SFAS 146.

Future minimum lease commitments, net of sublease income, are as follows:

Year Ending December 31,	
2005	$ 3,903,770
2006	5,546,538
2007	5,564,783
2008	4,911,431
2009	5,185,517
Thereafter	54,008,866
	$79,120,905

Under certain of the Company's collaborative agreements, it is obligated to make specified payments upon achieving specified milestones relating to the development and regulatory approval of Macugen. These contingent payment obligations are not included in the above table.

14. 401(k) Plan

The Company maintains a defined contribution 401(k) plan available to eligible employees. Employee contributions are voluntary and are determined on an individual basis, limited by the maximum amounts

allowable under federal tax regulations. The Company has discretion to make contributions to the plan. However, to date no contributions have been made.

15. Selected Quarterly Financial Data (Unaudited)

	Quarter Ended			
	March 31	June 30	September 30	December 31
2002				
Net loss	$ (8,747,753)	$ (9,631,821)	$(10,697,851)	$(14,096,037)
Net loss attributable to common stockholders	(9,833,552)	(10,717,620)	(11,971,922)	(15,746,650)
Basic and diluted net (loss) per common share*	$ (2.69)	$ (2.93)	$ (3.20)	$ (4.22)
2003*				
License fees	$ 833,334	$ 1,250,001	$ 1,250,001	$ 1,250,001
Reimbursement of development costs	6,475,830	9,948,756	11,143,313	9,267,930
Net loss	(5,422,172)	(9,071,789)	(14,308,255)	(11,897,029)
Net loss attributable to common stockholders	(7,681,135)	(11,330,753)	(16,583,830)	(14,263,909)
Basic and diluted net (loss) per common share*	$ (2.04)	$ (2.88)	$ (4.12)	$ (3.50)
2004				
License fees	1,250,000	1,250,000	1,407,613	1,814,884
Reimbursement of development costs	10,462,600	11,299,799	12,058,749	9,808,259
Net loss	(15,011,745)	(31,021,698)	(24,716,974)	(29,755,389)
Net loss attributable to common stockholders	(15,827,757)	(31,021,698)	(24,716,974)	(29,755,389)
Basic and diluted net (loss) per common share*	(0.57)	(0.77)	(0.60)	(0.72)

* 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.

Diluted EPS is identical to Basic EPS since common equivalent shares are excluded from the calculation as their effect is anti-dilutive.

16. Subsequent Event

In February 2005, in connection with the approval of Macugen by the FDA in December 2004, the Company issued to Pfizer 344,000 shares of common stock at a purchase price of approximately $43.60 per share. Gross proceeds of this sale were $15,000,000. Pfizer is not obligated to purchase any additional shares of the Company's common stock.

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Chairman of the Board of Directors

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Chief Executive Officer; Co-founder; Director

SRINIVAS AKKARAJU, M.D., PH.D.
Director

MARTY GLICK
Director

SAMIR PATEL, M.D.
Director

MICHAEL J. REGAN
Director

PHILLIP M. SATOW
Director

HENRY SIMON
Director

DAMION E. WICKER, M.D.
Director

Management

DAVID R. GUYER, M.D.
Chief Executive Officer

GLENN P. SBLENDORIO
Chief Financial Officer

PAUL G. CHANEY
Chief Operating Officer

ANTHONY P. ADAMIS, M.D.
Executive Vice President, Research and Development, Chief Scientific Officer

HAMED M. ABDOU, PH.D.
Senior Vice President, Technical Operations

HENRIC BJARKE
Senior Director, Marketing, Macugen Team Leader

CLARE M. CARMICHAEL
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CHRISTOPHER CARROLL, C.P.A.
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EMMETT T. CUNNINGHAM, JR., M.D., PH.D., M.P.H.
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LONI DA SILVA, M.S., RAC
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FRANCINE WINCOTT, PH.D.
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Corporate Information

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Our annual and quarterly reports filed with the Securities and Exchange Commission along with other corporate information will be furnished upon written request to Investor Relations at our corporate office.

Independent Certified Public Accountants

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MetroPark, NJ

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American Stock Transfer & Trust Company
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(Front Cover photo from left to right): Loni da Silva, Vice President, Global Regulatory Affairs; Harvey N. Masonson, M.D., Senior Director, Drug Safety and Clinical Development; Matthew Feinsod, M.D., Vice President, Strategy and Product Development; Karin Hehenberger, M.D., Ph.D., Senior Director, Scientific and External Affairs; Denis O'Shaughnessy, Ph.D., Senior Vice President, Clinical Research; Henric Bjarke, Senior Director, Marketing, Macugen Team Leader

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