UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

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

For Fiscal Year Ended December 31, 2003

or

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

From the transition period from_____ to _____

ISTA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**33-0511729**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

15279 Alton Parkway, Suite 100, Irvine, California 92618
(Address of principal executive offices)

(949) 788-6000
(Registrant's telephone number)

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

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

Common Stock, $.001 par value
(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 ☐

As of June 30, 2003, the aggregate market value of the Registrant's voting stock held by non-affiliates was approximately $22,053,000.

As of March 17, 2004 there were 17,456,678 shares of Common Stock outstanding.

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

DOCUMENTS INCORPORATED BY REFERENCE

None.

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ISTA PHARMACEUTICALS, INC.

PART I

References in this Annual Report on Form 10-K to "ISTA", "we", "our", "us" or the "Company" refer to ISTA Pharmaceuticals, Inc. This Form 10-K and the documents incorporated herein by reference contain forward-looking statements based on expectations, estimates and projections as of the date of this filing. Actual results may differ materially from those expressed in forward-looking statements. See Item 7 of Part II – "Management's Discussion and Analysis of Financial Condition and Results of Operations – Forward-Looking Statements."

Item 1: Business

Overview

ISTA was founded to discover, develop and market new remedies for diseases and conditions of the eye. Vitrase® (ovine hyaluronidase), is a proprietary drug we are developing for the treatment of vitreous hemorrhage, for use as a spreading agent to facilitate the dispersion and absorption of other drugs, and for the treatment of diabetic retinopathy. We are also developing other late-stage products, including Istalol™ (timolol) for the treatment of glaucoma, Xibrom™ (bromfenac) for the treatment of ocular inflammation, and Caprogel® (aminocaproic acid) for the treatment of hyphema.

In December 2001, we announced our strategic plan to transition from a development-stage organization to a specialty pharmaceutical company, with a primary focus on ophthalmology. We intend to execute this plan by continuing to advance products currently under development, and by acquiring complementary products, either already marketed or in late-stage development.

We continue to take significant steps to scale up our marketing and manufacturing capabilities, in order to further enhance our ability to execute our strategic plan. We entered into two key manufacturing agreements for the supply of commercial quantities of Vitrase® from Cardinal Health and Istalol™ and Xibrom™ from Bausch & Lomb Incorporated. We also added two senior management executives to bolster our financial, business and human resource capabilities: Lauren P. Silvernail, our Chief Financial Officer and Vice President, Corporate Development, and Kathleen McGinley, our Vice President, Human Resources and Corporate Services.

Vitrase® for the treatment of vitreous hemorrhage

In October 2002, we submitted to the U.S. Food and Drug Administration ("FDA") a New Drug Application ("NDA") for Vitrase® (ovine hyaluronidase) for the treatment of vitreous hemorrhage. On April 3, 2003, the FDA issued an approvable letter citing issues primarily related to the sufficiency of the efficacy data submitted with the NDA for Vitrase® for the treatment of vitreous hemorrhage. The FDA requested additional analysis of the existing data and an additional confirmatory clinical study based upon that analysis. We have submitted information to the FDA in response to its non-clinical comments contained in the approvable letter and are continuing to assess and discuss with the agency the clinical issues raised in the approvable letter. Based upon these discussions, we will determine the next appropriate steps in the approval process of Vitrase® for the treatment of vitreous hemorrhage.

Vitrase® for use as a spreading agent

In August 2003, we submitted to the FDA a second NDA for Vitrase® for use as a spreading agent to facilitate the dispersion and absorption of other drugs. The FDA granted "priority review" status for this NDA in August 2003 and accepted the NDA for filing and review in October 2003. In February 2004, the FDA notified us that it was extending the Prescription Drug User Fee Act ("PDUFA") action date 90 days to May 5, 2004. Based upon current discussions with the FDA, we believe that any remaining issues, and the FDA review, can be addressed within the revised time frame. The product submitted in the second NDA is the same formulation as the product submitted in the original NDA. The dose used as a spreading agent is different than the dose used for injection into the back of the eye. With respect to the second Vitrase® NDA, we are pursuing the development of additional package configurations for different doses of the product to facilitate product utilization, improve profit margins and aid in third-party reimbursement. Upon approval of the second Vitrase® NDA, we intend to submit supplemental filings with the FDA with respect to such additional package and dosage configurations.

Other Product Candidates

In May 2002, we acquired substantially all of the assets of AcSentient, Inc., which included United States marketing rights for two ophthalmic products and worldwide rights for a third. The products with United States rights included Istalol™, a new once-a-day formulation of timolol for the treatment of glaucoma, and Xibrom™, a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation. We also received worldwide marketing rights for

Caprogel®, a novel compound for the treatment of hyphema. Our rights to Istalol™ and Xibrom™ are licensed from Senju Pharmaceuticals Co., Ltd., a Japanese pharmaceutical company, and our rights to Caprogel® are licensed from the Eastern Virginia Medical School.

The NDA for Istalol™ was submitted to the FDA in September 2002 and was accepted for review in November 2002. We received an approvable letter from the FDA for Istalol™ in July 2003, and we expect FDA approval of Istalol™ in the first half of 2004. We completed our Phase III studies of Xibrom™ and announced initial results of our clinical studies in March 2004. Based on the initial results of our Phase III studies, we anticipate submitting a NDA for Xibrom™ in the second quarter of 2004. We are currently conducting feasibility studies for the reformulation and commercialization of Caprogel®. We anticipate incurring additional research and development expenses in connection with the final development of Xibrom™ and Caprogel®, and if these compounds are approved for sale in the United States, we expect to incur significant marketing and sales expenses. In addition, we will also be responsible for certain milestone payments to Senju in connection with the marketing approval in the United States for these compounds.

Our Strategy

Our objective is to build a specialty pharmaceutical company focused on serious diseases and conditions of the eye. We intend to capitalize on our management's collective experience developing and commercializing ophthalmic products with goals to:

- Gain regulatory approval and market acceptance for our existing late-stage ophthalmic product candidates;
- Build a commercial infrastructure to support multiple ophthalmic product launches;
- Conduct business development efforts to further expand our late-stage product pipeline; and
- Pursue opportunistic acquisitions of marketed products.

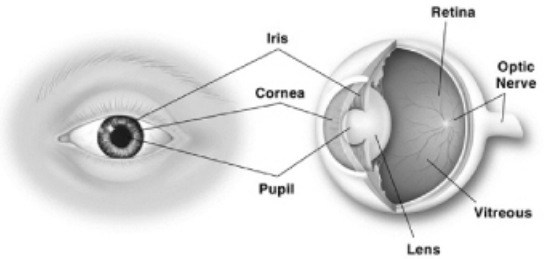
Follow-On Public Offering

On November 12, 2003, we completed a follow-on public offering of 4,000,000 shares of common stock at an offering price of $9.50 per share with gross proceeds of $38,000,000. Net proceeds, after a 6% underwriters discount and other offering expenses, were $35,169,000. Additional expenses relating to the follow-on public offering, other than the underwriters discount, were approximately $551,000. The managing underwriters for the offering were Thomas Weisel Partners LLC, Jefferies & Company, Inc., RBC Capital Markets and Roth Capital Partners. The shares of common stock sold in this offering were registered on Form S-2, as amended (File No. 333-109576).

Anatomy of the Eye

The human eye is approximately one inch in diameter and functions much like a camera. The eye incorporates a lens system (the cornea and the lens) that focuses light, a variable aperture system (the iris) that controls the amount of light passing through the eye and a film (the retina) that records the image. The cornea, lens and iris operate to focus light rays on the retina, which contains the receptors that transmit images through the optic nerve to the brain.

The cavity between the lens and the retina is filled with the vitreous humor, a clear, gel-like substance. The vitreous humor is nearly solid in children and undergoes a natural transition to liquid as one ages.



Cornea: The clear, transparent outer portion of the front of the eye that provides most of the eye's focusing power.

Iris: The colored part of the eye that helps control the amount of light that enters the eye.

Pupil: The dark hole in the middle of the iris through which light enters the eye.

Lens: The transparent structure inside the eye (behind the cornea and iris) that also focuses light rays onto the retina.

Vitreous: The clear, gel-like substance that fills the back of the eye between the lens and the retina. It is principally made up of hyaluronan, a high molecular weight proteoglycan.

Retina: The nerve layer that lines the back of the eye. The retina senses light and transmits impulses that are sent through the optic nerve to the brain.

Optic nerve: The nerve that connects the eye to the brain and carries the impulses formed by the retina.

Product Development Programs

We have four product candidates covering six indications in clinical development. The following is a summary of our clinical product candidates:

Product	Indication	Development Status
Vitrase®	Vitreous hemorrhage	FDA Approvable Letter Received
Vitrase®	Spreading agent	NDA Accepted and Priority Review Status Granted. PDUFA action date: May 5, 2004
Vitrase®	Diabetic retinopathy	Phase II
Istalol™	Glaucoma	FDA Approvable Letter Received
Xibrom™	Ocular inflammation	Phase III
Caprogel®	Hyphema	Reformulation Ongoing

Vitrase®

We are developing Vitrase®, a proprietary formulation of ovine hyaluronidase, for the treatment of vitreous hemorrhage, for use as a spreading agent, and for diabetic retinopathy. The term hyaluronidase describes a group of naturally occurring enzymes that can digest certain forms of carbohydrate molecules called proteoglycans. When injected into the vitreous humor, Vitrase® breaks down the proteoglycan matrix, causing the vitreous humor to liquefy. We believe that this also results in the separation of the vitreous humor from the retina and that, together, these effects are beneficial for the treatment of vitreous hemorrhage and diabetic retinopathy. Vitrase® may be administered directly into the vitreous humor through a single-dose injection. The procedure is performed in several minutes in an ophthalmologist's office and is virtually painless due to the application of a topical anesthetic. Vitrase® can also be injected into connective tissue, where it modifies the permeability of such tissue through the hydrolysis of hyaluronic acid, thereby decreasing the viscosity of the cellular cement and promoting diffusion of injected fluids or localized transudates or exudates, thus facilitating their absorption.

Vitreous Hemorrhage. A vitreous hemorrhage occurs when retinal blood vessels rupture and bleed into the vitreous humor. These hemorrhages result from leakage from abnormal, weak blood vessels and are associated with diabetic retinopathy, trauma and other factors. The immediate consequence of a vitreous hemorrhage is a reduction in the amount of light that can pass through the normally clear vitreous humor to the retina. The effects of a hemorrhage can be limited to a few dark spots in vision or, in the case of a severe vitreous hemorrhage, can result in completely obscured vision. Depending on the severity of the vitreous hemorrhage, it may take several months or significantly longer for the body to reabsorb the blood and for the patient to regain vision. In addition to obstructing the patient's vision, a vitreous hemorrhage often prevents physicians from seeing into the back of the eye to diagnose or treat the cause of the hemorrhage. If extensive or repeated bleeding occurs, fibrous tissue or scarring can form on the retina, which can lead to a detachment of the retina and permanent vision loss or blindness.

Patients who seek medical care for a vitreous hemorrhage often visit a physician, who then refers them to a retinal specialist. Treatment options for patients with a vitreous hemorrhage are limited. Currently, there is no drug treatment for vitreous hemorrhage and most retinal specialists initially recommend a "watchful waiting" period, during which the attending physician provides no medical treatment in the hope that the hemorrhage will clear on its own. The risks related to watchful waiting may include continued bleeding and, if caused by diabetic retinopathy, disease progression during the time it takes for the blood to clear on its own, if at all.

An alternative to watchful waiting is a surgical procedure called a vitrectomy, in which the vitreous humor and hemorrhage are surgically removed and replaced with a balanced salt solution. There are serious risks associated with a vitrectomy, including both cataract formation and possible loss of vision associated with retinal detachment. These risks contribute to the limited use of vitrectomy as an initial treatment option for vitreous hemorrhage patients.

Vitrase® is being developed to promote clearance when injected into a blood-filled vitreous humor by causing the vitreous humor to liquefy and the blood to settle to the bottom of the eye. Vitrase® may also stimulate the cells responsible for engulfing and breaking down the blood, accelerating the reabsorption of the blood. This would clear the path for light to reach the retina and may enable the patient to regain vision. In addition, clearing the hemorrhage permits the retinal specialist to visualize, diagnose and treat the underlying cause of the vitreous hemorrhage.

Hemorrhage density can vary significantly between patients who experience vitreous hemorrhage, but even a mild hemorrhage indicates the existence of a serious problem. Because of the absence of a validated and generally accepted medical definition of the various densities of vitreous hemorrhage, we classify a vitreous hemorrhage as either mild, moderate or severe depending on the density of the vitreous hemorrhage as observed by the physician:

- mild vitreous hemorrhage is characterized by trace blurring of retinal blood vessels;
- moderate vitreous hemorrhage is characterized by partial obscuration of retinal blood vessels and/or the optic nerve; and
- severe vitreous hemorrhage is characterized by complete obscuration of retinal blood vessels and/or the optic nerve.

Market Opportunity. Based on data compiled by Business Genetics, Inc., we believe that approximately 450,000 cases of vitreous hemorrhage occur each year in the United States, a total of 400,000 cases occur each year in the five largest European markets and 190,000 cases occur each year in Japan. Approximately 60% of all of these cases are due to diabetic retinopathy, 15% are due to trauma and 25% are due to other factors. As a result of the typical progression of the disease, we believe Vitrase®, if approved, is unlikely to be used in all cases of vitreous hemorrhage. Based on data compiled for us by The Wilkerson Group, we believe that approximately half of all cases are candidates for treatment using Vitrase®.

Clinical/Regulatory Status. In October 1998, the FDA granted fast-track designation for Vitrase® for the treatment of vitreous hemorrhage. The FDA's provision for "fast-track" designated drugs, such as Vitrase®, provides for early submission of completed sections of the NDA. In January 2002, as a part of our rolling NDA for Vitrase® for the treatment of vitreous hemorrhage, we submitted the pre-clinical pharmacology and toxicology section.

We have completed two Phase III clinical trials of Vitrase® for the treatment of vitreous hemorrhage. These trials were prospective, randomized, parallel, placebo-controlled and double-masked studies. We conducted one of the trials, our North America trial, in the United States, Mexico and Canada with an enrollment of 750 patients. We conducted the other trial in Europe, Brazil, Australia and South Africa with an enrollment of 556 patients. Patients enrolled in the studies were monitored through 2003. We contracted with CroMedica Global, Inc. in connection with the North America trial and Covance Clinical Periapproval Services, Inc. in connection with the Europe, Brazil, Australia and South Africa trial to provide certain management and support services, including initiation visits with prospective candidates, site management, data accumulation, drug supply management and site audits.

In both studies, we enrolled patients who had both a vitreous hemorrhage that had been present for at least one month and a Best Corrected Visual Acuity ("BCVA") of less than 20/200 at initial screening. After enrollment, patients were randomly assigned to either a test group or a control group. Patients in the test group received either a 7.5 (North America only), 55 or 75 international unit, or IU, injection of Vitrase®. Patients in the control group received a saline injection. The primary (surrogate) endpoint in both studies was defined by the clearance of the vitreous hemorrhage sufficient to allow for the occurrence of any one of the following, which must have occurred within three months following treatment with Vitrase®:

- panretinal laser photocoagulation surgery to slow or stop the cause of the vitreous hemorrhage;
- other surgical treatment not specifically indicated for the clearance of the vitreous hemorrhage (for example, vitrectomy to enable treatment of retinal detachment); and
- documented medical evidence that the clinical cause of the vitreous hemorrhage has been resolved without the need for further therapy.

Additionally, at each study visit and specifically at months one, two and three following treatment, BCVA was assessed using an eye chart in both studies.

In March 2002, we announced the preliminary results for our Phase III clinical studies of Vitrase® for the treatment of vitreous hemorrhage. The data from the two Phase III studies did not show a statistically significant improvement in the primary (surrogate) endpoint. However, further analysis has shown that for the 55 IU dose of Vitrase®, in both studies, there was a clinically meaningful and statistically significant decrease in the density of vitreous hemorrhage and a statistically significant difference in the proportion of patients with an improvement in best-corrected visual acuity at one and two months, which extended to the three-month post-treatment visit in the study conducted outside North America. Based on these improvements in visual function, and our review and discussions with the FDA regarding the data from the two studies, we submitted the clinical section and the chemistry, manufacturing and controls ("CMC") section of the NDA for Vitrase® for the treatment of vitreous hemorrhage in October 2002. The FDA accepted those sections of the Vitrase® NDA for review in December 2002, along with the pre-clinical pharmacology and toxicology section that was submitted in January 2002. On April 3, 2003, the FDA issued an approvable letter in which the FDA cited issues primarily related to the sufficiency of the efficacy data submitted with the NDA for Vitrase®. The FDA requested additional analysis of the existing data and an additional confirmatory clinical study based upon that analysis. We have submitted information to the FDA in response to its non-clinical comments contained in the approvable letter and are continuing to assess and discuss with the agency the clinical issues raised in the approvable letter. Based upon these discussions, we will determine the next appropriate steps in the approval process of Vitrase® for the treatment of vitreous hemorrhage.

Spreading Agent. Hyaluronidase has been found to be a spreading or diffusing substance, which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronidase temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids or of localized transudates or exudates, thus facilitating their absorption.

When no spreading factor is present, material injected subcutaneously spreads very slowly, but hyaluronidase causes rapid spreading, provided local interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by injected solutions. The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution.

Market Opportunity. Based on data compiled in reports published by the American Academy of Ophthalmology, we estimate that a previously marketed hyaluronidase product was used in approximately 750,000 ophthalmic surgery cases annually, when it was commercially available.

Clinical/Regulatory Status. In August 2003, we submitted to the FDA a second NDA for Vitrase® for use as a spreading agent to facilitate the dispersion and absorption of other drugs. The FDA granted "priority review" status for this NDA in August 2003 and accepted the NDA for filing and review in October 2003. In February 2004, the FDA notified ISTA that it was extending the PDUFA action date 90 days to May 5, 2004. The product submitted in the second NDA is the same formulation as the product submitted in the original Vitrase® NDA for the treatment of vitreous hemorrhage. The dose used as a spreading agent is different than the dose used for injection into the posterior region of the eye. With respect to the second Vitrase® NDA, we are pursuing the development of additional package configurations for different doses of the product to facilitate product utilization, improve profit margins and aid in obtaining appropriate third-party reimbursement. Upon approval of the second Vitrase® NDA, we intend to submit supplemental filings with the FDA with respect to such additional package configurations.

Diabetic Retinopathy. Abnormal changes and/or damage to the blood vessels in the eye due to diabetes are known as diabetic retinopathy. Diabetic retinopathy is a progressive disease consisting of two stages, nonproliferative and proliferative. Nonproliferative diabetic retinopathy is the first stage of diabetic retinopathy and occurs when the retinal blood vessels swell and leak fluid and small amounts of blood into the eye.

We believe that Vitrase® can treat diabetic retinopathy at the nonproliferative stage. Following injection into the vitreous humor, Vitrase® acts to separate the vitreous humor from the retina, thereby limiting growth of retinal blood vessels into the vitreous humor. We believe that Vitrase® achieves this by breaking down the proteoglycan component of the substance that binds the vitreous humor to the retina and by liquefying the vitreous humor. This process allows the vitreous humor to detach from the retina. Retinal specialists consider this detachment to be beneficial to diabetic retinopathy patients because it may delay the progression of the disease.

Market Opportunity. Diabetes continues to be a major healthcare problem in the United States, and we project it to continue growing rapidly in many regions outside the United States. Eye disease is commonly associated with diabetes. Based on our market research, we believe that nearly eight million individuals in the United States have been diagnosed with diabetes, four to six million have some form of diabetic retinopathy, and that the majority of individuals with diabetic

retinopathy are in the nonproliferative stage of the disease. We believe that these people are potential candidates for treatment using Vitrase®.

Clinical/Regulatory Status. We have completed a 60 patient pilot Phase II clinical trial in Mexico City to evaluate the safety and efficacy of a single-dose injection of Vitrase® to cause a detachment of the vitreous humor from the retina and the impact on slowing the progression of diabetic retinopathy over a one-year period.

The continued development of Vitrase® for the treatment of diabetic retinopathy will be dependent upon a number of factors including, among others, the FDA's evaluation of the Vitrase® NDA for the treatment of vitreous hemorrhage and for use as a spreading agent, the successful completion of any additional clinical trials for the diabetic retinopathy indication and the continuing assessment of the market opportunity for this indication as compared to other product opportunities we may be pursuing at the time.

Istalol™ (timolol)

Istalol™ is our once-daily, topical solution of timolol, a beta-blocking agent for the treatment of glaucoma. The product was developed by Senju in Japan. In May 2002, as part of the AcSentient asset acquisition, we acquired marketing rights for Istalol™ in the United States.

Glaucoma is a disease that gradually reduces eyesight without warning and often without symptoms. Vision loss is caused by damage to the optic nerve. Glaucoma is a chronic disease that must be treated for life. Currently, its causes are not well understood and there is no cure.

Market Opportunity. According to prescription data compiled by NDC Health, we estimate that the United States pharmaceutical market for the treatment of glaucoma exceeds $1.1 billion per year. According to data compiled by NDC Health, we estimate the U.S. ophthalmic beta-blocker market exceeds $170 million per year, with over 4.4 million prescriptions written annually.

Clinical/Regulatory Status. Senju submitted a NDA for Istalol™ to the FDA in September 2002 that was accepted for review in November 2002. The NDA is based on data from a Phase I clinical study and a multi-center Phase III clinical trial completed in the United States. In July 2003, the FDA issued an approvable letter with respect to the Istalol™ NDA citing issues related to manufacturing methods and controls. No additional clinical studies were requested. We believe the issues cited by the FDA are addressable, and we are currently seeking qualification of an additional manufacturing site. In December 2003, we submitted documents to the FDA seeking to qualify Bausch & Lomb as an alternate manufacturer of Istalol™. We expect FDA approval of Istalol™ in the first half of 2004.

In the clinical trials, Istalol™ has shown efficacy and safety comparable to timolol maleate, which is the leading beta-blocker to treat glaucoma in the United States. Advantages of Istalol™ include enhanced corneal penetration and once-daily administration. Third-party formulations of timolol currently on the market are twice-daily solutions or gel formulations, which are known to cause blurring of patients' vision.

Xibrom™ (bromfenac)

Xibrom™ is a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation. The product was developed by Senju in Japan. Senju launched Xibrom™ in Japan in 2000, and we believe its rapid sales growth in Japan is principally due to its superior potency and twice-daily dosing regimen, as compared to the requirement of four doses-per-day for most other anti-inflammatory products on the Japanese market. In May 2002, as part of our AcSentient asset acquisition, we acquired marketing rights for Xibrom™ in the United States.

Market Opportunity. According to prescription data compiled for us by IMS Health, we estimate that the current global ophthalmic anti-inflammatory and allergies markets to be approximately $500 million and $630 million per year, respectively. Currently in the U.S., we estimate that there are over 5.4 million prescriptions written annually for topical ophthalmic anti-inflammatory agents.

Clinical/Regulatory Status. Phase I, Phase II and Phase III clinical studies of Xibrom™ have been completed in Japan and the product has been approved and was launched in 2000 in Japan. In December 2003, we completed enrollment of our Phase III clinical studies in the United States and announced initial results of our clinical studies in March 2004. In two double-masked, placebo-controlled U.S. Phase III studies conducted under a single protocol, a statistically significant proportion of patients treated with Xibrom™ achieved treatment success as compared to placebo. Treatment success was defined as the complete absence of ocular inflammation. In one study involving 296 patients at 20 study sites, more Xibrom™ -treated patients cleared their ocular inflammation at 15 days when compared to patients receiving placebo at a rate of 62.6% versus 39.8%, respectively. In a second U.S. study, which involved 231 patients at 19 study sites, the rates of ocular

inflammation clearance at the primary endpoint of 15 days were 65.8% for Xibrom™ -treated patients and 47.9% for patients receiving placebo. Statistical significance in each trial reached a p value of less than 0.01. Our analyses showed that the Xibrom™ treatment effect was evident as early as day three in both trials. The primary endpoint for both studies was the proportion of patients with complete absence of ocular inflammation, as measured by an assessment of immune cells in the anterior chamber of the eye and cellular debris. For each trial, the secondary efficacy analysis of inflammation clearance in patients only on assigned treatment (with no other medications administered) also showed a statistically significant benefit for Xibrom™ treatment at 15 days versus placebo. In the 20-site study, the rates of clearance were 57.6% for Xibrom™ and 23.5% for placebo. In the 19-site study, the rates of clearance were 62.0 % for Xibrom™ and 31.5 % for placebo. Both studies, when analyzed separately, also showed that Xibrom™ was well tolerated with a very low incidence of ocular adverse events. The efficacy and safety findings were consistent with results of previous studies conducted in Japan by Senju.

Caprogel® (aminocaproic acid)

Caprogel® is a new topical gel formulation of amniocaproic acid for treating hyphema. In May 2002, as part of our AcSentient asset acquisition, we acquired AcSentient's worldwide marketing rights for Caprogel®. The product is licensed from the Eastern Virginia Medical School.

Hyphema is a term used to describe bleeding in the anterior chamber, the space between the cornea and the iris, of the eye. It occurs when blood vessels in the iris bleed and leak into the clear aqueous fluid and typically results from trauma to the eye. Hyphemas are usually characterized by pooling of blood in the anterior chamber that may be visible to the naked eye. The red blood cells of very small hyphemas are visible only with magnification. Even the slightest amount of blood in the anterior chamber will cause decreased vision when mixed in the clear aqueous fluid.

Some of the symptoms of hyphema are decreased vision, depending on the amount of blood in the eye, pooling of blood in the anterior chamber and elevated intraocular pressure. A doctor will assess visual acuity, measure intraocular pressure and examine the eye with a split lamp microscope and ophthalmoscope.

The treatment is dependent on the cause and severity of the hyphema. Frequently, the blood is reabsorbed over a period of days to weeks. During this time, the doctor will carefully monitor the intraocular pressure for signs of the blood preventing normal flow of the aqueous fluid through the eye's angle structures. If the eye pressure becomes elevated, eye drops may be prescribed to control it. The pupils are also evaluated to rule out damage to the iris. In some cases, a procedure is performed to irrigate the blood from the anterior chamber to prevent secondary complications such as glaucoma and bloodstains on the cornea.

Market Opportunity. Based on data compiled for us by Milliman U.S.A., we believe that hyphema affects an estimated 50,000 patients per year in the United States and currently there is no available pharmaceutical agent approved for its treatment.

Clinical/Regulatory Status. We are currently conducting feasibility studies for the reformulation and commercialization of Caprogel®. Once completed, and if these studies yield promising results, we intend to pursue further clinical development of Caprogel® consistent with such studies' results. However, the timing and scope for our development of Caprogel® may change based on a number of factors, including, among others, our assessment, from time to time, of this product's clinical results, market potential, other product opportunities and our corporate priorities. Caprogel® has received an orphan drug designation for the treatment of hyphema from the FDA, which may result in us receiving a seven year market exclusivity privilege with respect to Caprogel®, if approved.

Other Product Candidates

We continually evaluate new opportunities for complementary product candidates and, if and when appropriate, intend to pursue such opportunities through further product acquisitions and related development activities. Our ability to execute on such opportunities in some circumstances will be dependent, in part, upon our ability to raise additional capital on commercially reasonable terms.

Collaborations

Collaboration With Allergan

In March 2000, we began a collaboration with Allergan, Inc. with respect to the development and commercialization of Vitrase® worldwide (other than in Mexico until April 2004 and Japan) for ophthalmic uses for the posterior region of the eye, a supply agreement for Vitrase® and a stock purchase agreement for $10.0 million of our Series D preferred stock. These shares of Series D preferred stock were subsequently converted into 102,407 shares of our common stock. Allergan is a leading provider of eye care and specialty pharmaceutical products throughout the world. A joint operating committee has

been constituted and consists of an equal number of members from each company who will oversee development, regulatory and marketing activities with respect to Vitrase® for ophthalmic uses in the posterior region of the eye, as more fully described below.

Under the terms of our agreements with Allergan:

- *Development.* We have an obligation to use commercially reasonable efforts to obtain regulatory approval for Vitrase® in the United States and Europe, and Allergan is responsible for commercializing Vitrase® for uses in the posterior region of the eye. We are also responsible for all product development, preclinical studies and clinical trials in support of marketing approvals of Vitrase® for the treatment of vitreous hemorrhage in the United States and Europe. We are also responsible for all preclinical studies and clinical trials to demonstrate the safety and efficacy of Vitrase® for the treatment of diabetic retinopathy.

- *Regulatory Approvals.* We are responsible for applying for and obtaining regulatory approval of Vitrase® for such treatments in the United States and in the European Union. Allergan will be responsible for applying for and obtaining regulatory approvals of Vitrase® for such treatments in markets outside the United States and the European Union where it deems appropriate, other than Mexico (until April 2004) and Japan.

- *Manufacturing.* We are responsible for the manufacture of Vitrase® and, if approved, for supplying all of Allergan's requirements for Vitrase® during the term of the license agreement.

- *Marketing.* In the United States, Allergan will be responsible for the overall management of marketing, sale and distribution activities for Vitrase® for ophthalmic uses in the posterior region of the eye through its established sales and marketing organization. Under the terms of the license agreement, we will employ medical specialists in the United States to assist in physician training and usage development. In all markets outside the United States, except Mexico and Japan, Allergan will be solely responsible for the marketing, sale and distribution of Vitrase® for ophthalmic uses in the posterior region of the eye. Allergan has exclusive rights in all countries of the world, except Mexico and Japan, to the Vitrase® trademark in connection with its marketing of such product. We are currently in discussions with Allergan regarding marketing and other strategies in the event the FDA approves our NDA for Vitrase® for use as a spreading agent. Allergan has informed us of its position that we need its authorization pursuant to our collaboration to market Vitrase® on our own as a spreading agent, which Allergan asserts has not been provided. In addition, Allergan may be unwilling to pursue the marketing and commercialization of Vitrase® with any final approved labeling that does not meet its satisfaction.

- *Milestone Payments.* Allergan has agreed to pay us an aggregate amount of up to $35.0 million in milestone payments based on our achievement of specified regulatory and development objectives with respect to Vitrase® for the treatment of vitreous hemorrhage and diabetic retinopathy. To date, we have not earned any milestone payments from Allergan, and we cannot guarantee that we will earn or receive any future milestone payments.

- *Profit Sharing and Royalties.* In the United States, we will share profits on the sale of Vitrase® with Allergan on a 50/50 basis during the term of the license agreement. In all markets outside the United States, except Mexico (until April 2004) and Japan, we will receive a royalty on all sales of Vitrase® by Allergan.

- *Term and Termination.* Allergan's license to market, sell and distribute Vitrase® is limited to the ophthalmic uses in the posterior regions of the eye. Allergan's license in the United States will expire ten full calendar years following the date of the first commercial sale of Vitrase® for a licensed use, at which time all commercial rights for Vitrase® in the United States will revert to us. Allergan's obligation to pay royalties will terminate on a country-by-country basis upon the latest of 10 full calendar years following the date of the first commercial sale in each particular country and the expiration date of the last-to-expire licensed patent relating to Vitrase® in that country. Allergan may terminate the license agreement at any time with three months notice to us. We may terminate the license agreement on a country-by-country basis in certain countries if Allergan fails to commercialize Vitrase® within 12 months of regulatory approval in that country.

- *Board of Director Representation and Visitation Rights.* Allergan has the right to request that we nominate an Allergan representative to our Board of Directors. In the event that the Allergan nominee is not elected to the Board of Directors, Allergan has certain visitation rights, which include the designation of an Allergan representative to attend and observe all of our Board of Director meetings.

Collaboration With Otsuka

In December 2001, we began a collaboration with Otsuka Pharmaceutical Co., Ltd. with respect to the commercialization of Vitrase® in Japan for ophthalmic uses in the posterior region of the eye, including a license agreement for the clinical development, regulatory approval, marketing, sale and distribution of Vitrase®, a supply agreement for Vitrase® and a securities purchase agreement for 84,567 shares of our common stock for the aggregate purchase price of $4.0 million. Otsuka is part of the Otsuka Group, headquartered in Tokyo, Japan and has a diverse portfolio including ophthalmic, central nervous system, cardiovascular, circulatory, gastro-intestinal, respiratory, oncological and dermatological products.

Under the terms of our agreements with Otsuka:

- *Clinical Development.* Otsuka is responsible for all preclinical studies and clinical trials in support of marketing approval of Vitrase® for the treatment of vitreous hemorrhage in Japan. Otsuka is also responsible for all preclinical studies and clinical trials for regulatory approvals for additional indications including the treatment of diabetic retinopathy.

- *Regulatory Approvals.* Otsuka is responsible for applying for and obtaining regulatory approval of Vitrase® for such treatments in Japan. Otsuka will also be responsible for obtaining National Health Insurance pricing approval for Vitrase® from the Japanese Ministry of Health. We will be responsible for providing Otsuka with copies of preclinical and clinical data and study reports and other documents in connection with our regulatory filings for Vitrase® in the United States.

- *Manufacturing.* We are responsible for the manufacture of Vitrase® and for the supply of all of Otsuka's requirements for clinical trials in Japan. If approved, we will also be responsible for supplying all of Otsuka's commercial product requirements for Vitrase® during the term of the license agreement.

- *Marketing.* Otsuka will be responsible for the overall management of marketing, sales and distribution activities for Vitrase® for ophthalmic uses in the posterior region of the eye in Japan through its established sales and marketing organization.

- *Milestone Payments.* Otsuka paid us a non-refundable license fee of $5.0 million as part of the license agreement. Otsuka has also agreed to pay us a milestone payment of $10.0 million upon regulatory approval of Vitrase® for the treatment of vitreous hemorrhage in Japan. To date, we have not earned this milestone payment from Otsuka and we cannot guarantee that we will earn or receive this milestone payment in the future.

- *Commercial Purchase of Vitrase®.* Otsuka is required to purchase Vitrase® from us at a percentage of the annual National Health Insurance price as established for Vitrase® in Japan during the term of the license agreement, unless we are unable to supply Vitrase® to Otsuka. If we are unable to supply Vitrase® to Otsuka and Otsuka, or a third party, is required to manufacture Vitrase® to meet Otsuka's supply requirements, we will only receive a royalty on sales of Vitrase® by Otsuka.

- *Term and Termination.* Otsuka's license to Vitrase® is limited to the ophthalmic uses in the posterior region of the eye and the territory of Japan. Our agreements with Otsuka will terminate upon the latest of 15 full calendar years following the date of the first commercial sale of Vitrase® for licensed uses in Japan and the expiration date of the last-to-expire licensed patent relating to Vitrase® for licensed uses in Japan. Otsuka may terminate the agreements at any time with six months notice to us. We may terminate the agreements if Otsuka fails to submit an application for regulatory approval of Vitrase® in Japan within 12 months of completing all necessary clinical trials and the initial meeting with the Japanese Ministry of Health to review the clinical trial results.

Collaboration With Senju

In May 2002, we expanded our late-stage product portfolio, acquiring three promising therapeutic products with ophthalmic applications from AcSentient. The costs associated with this acquisition were approximately $1.7 million. Two of the three products, Istalol™ and Xibrom™, were products developed by Senju. As a result of this acquisition, we began a collaboration with Senju including individual license agreements for the commercialization of Istalol™ and Xibrom™ in the United States. These license agreements were originally executed between Senju and AcSentient. The full rights and obligations of AcSentient under both license agreements were transferred to us as a part of the acquisition agreement between us and AcSentient, with such transfer approved by Senju.

Under the terms of our agreements with Senju:

- *Clinical Development.* Senju is responsible for completing development activities for Istalol™. We are responsible for completing development activities for Xibrom™.

- *Regulatory Approvals.* Senju was responsible for preparing and submitting a NDA to the FDA for Istalol™. Senju submitted this NDA in September 2002. In July 2003, the FDA issued an approvable letter with respect to the Istalol™ NDA citing issues related to manufacturing methods and controls. No additional clinical studies were requested. In December 2003, we submitted documents to the FDA seeking to qualify Bausch & Lomb as an alternate manufacturer of Istalol™. We expect FDA approval of Istalol™ in the first half of 2004. We completed our Phase III studies of Xibrom™ and announced initial results of our clinical studies in March 2004. Based on the initial results of our Phase III studies, we anticipate submitting a NDA for Xibrom™ in the second quarter of 2004. All follow-up activities with the FDA for both Istalol™ and Xibrom™ will be handled by us.

- Manufacturing. We will be responsible for the manufacture of Istalol™ and Xibrom™.

- *Marketing.* We will be responsible for the overall management of marketing, sales and distribution activities for Istalol™ and Xibrom™ in the United States.

- Milestone *Payments and Royalties.* We will be required to pay to Senju (i) non-refundable milestone payments of up to $4,000,000, some of which has been paid, if all such milestones, relating to the development process and regulatory approval of both Istalol™ and Xibrom™, are accomplished; and (ii) royalties on product sales.

- *Term and Termination.* The license agreements with Senju will terminate upon the last-to-expire licensed patent in the United States relating to Istalol™ and ten years after the first commercial sale of Xibrom™ in the United States, respectively. Neither party is entitled to terminate the agreements without cause.

Collaboration With the Eastern Virginia Medical School

In May 2002, as part of our AcSentient asset acquisition, we acquired worldwide marketing rights for Caprogel®. Caprogel® was initially licensed by AcSentient from the Eastern Virginia Medical School. The full rights and obligations of AcSentient under the Eastern Virginia Medical School license agreement were assigned to us as a part of the acquisition agreement between us and AcSentient, with such transfer approved by the Eastern Virginia Medical School.

Under the terms of our agreements with the Eastern Virginia Medical School:

- *Clinical Development.* We are responsible for completing development activities for Caprogel®. We are currently conducting feasibility studies for the reformation and commercialization of Caprogel®. Once completed, and if these studies yield promising results, we intend to pursue further clinical development of Caprogel® consistent with such studies' results. However, the timing and scope for our development of Caprogel® may change based on our assessment, from time to time, of this product candidate's market potential, other product opportunities and our corporate priorities.

- *Regulatory Approvals.* We are responsible for the preparation and submission of an NDA to the FDA for Caprogel® assuming the successful conclusion of our clinical study efforts. All follow-up activities with the FDA for Caprogel® will be handled by us.

- Manufacturing. We will be responsible for the manufacture of Caprogel®.

- Marketing. We will be responsible for the overall management of marketing, sales and distribution activities for Caprogel® on a worldwide basis.

- Royalties. The Eastern Virginia Medical School will receive royalty payments on all sales of Caprogel® by us worldwide.

- *Term and Termination.* The license agreement with the Eastern Virginia Medical School will terminate upon the last-to-expire licensed patent in the United States relating to Caprogel®. We may terminate the license agreement with the Eastern Virginia Medical School upon three months prior written notice.

Marketing and Sales

Assuming receipt of applicable regulatory approvals, we plan to market and distribute Vitrase® (spreading agent indication), Istalol™, Xibrom™ and Caprogel® in the United States ourselves. We will therefore need to establish our own sales, marketing and distribution capabilities, through our own internal resources and/or through contract arrangements with third parties We will need to devote significant financial and management resources to develop such sales, marketing and distribution capabilities. We plan to target our commercialization efforts to the most prolific prescribers of ophthalmic beta-blockers, non-steroidal anti-inflammatories and the highest volume cataract surgeons. This focused activity is intended to maximize our reach into the market opportunity for each product, if and when they are approved. We also may commercialize a hyaluronidase product under a trade name other than Vitrase® for use as a spreading agent directly to physicians via our new targeted sales force. Such plans are dependent upon FDA approval of our second Vitrase® NDA, FDA approval of a dosage configuration for use only as a spreading agent, obtaining appropriate third-party reimbursement, Allergan's rights under our collaboration with respect to Vitrase® for uses in the posterior region of the eye and the market potential of Vitrase® for use as a spreading agent and our corporate priorities.

In addition, assuming receipt of applicable regulatory approvals, we plan to market and distribute Vitrase® for use in the posterior region of the eye through our collaboration with Allergan in the United States and all international markets, except Mexico (until April 2004) and Japan. We have a distribution agreement with Laboratorios Sophia S.A. de C.V. providing for the marketing, sales and distribution of Vitrase® in Mexico until April 2004. Pursuant to our agreement with Laboratorios Sophia, we are entitled to 75% of the final retail price for all sales of Vitrase® by Laboratorios Sophia. The agreement with Laboratorios Sophia may not be terminated by either party without cause. We have an agreement with Otsuka providing for the development and commercialization of Vitrase® for ophthalmic uses in the posterior region of the eye in Japan. In the United States, the primary target market for Vitrase® for the treatment of vitreous hemorrhage is expected initially to be retinal specialists to whom most patients with vitreous hemorrhage are referred. For the use of Vitrase® as a spreading agent, the primary market will be cataract surgeons.

Third-party Reimbursement

In the United States, physicians, hospitals and other healthcare providers that purchase pharmaceutical products generally rely on third-party payers, principally private health insurance plans, Medicare and, to a lesser extent, Medicaid, to reimburse all or part of the cost of the product and procedure for which the product is being used. Currently, a Current Procedural Terminology ("CPT") code has been established for the intravitreal injection of a pharmaceutical agent, which, we believe, will be appropriate for physician billing for a Vitrase® injection. This code may result in reimbursement for the physician's services in administering the drug, but will not result in reimbursement for the drug itself. Drug specific coverage policies are primarily developed by Medicare carriers following Medicare's criteria for drug coverage, which include, among other requirements, that the drug be FDA-approved, be used in connection with a physician service and be medically reasonable for the treatment of an illness or injury. While reimbursement may be available under existing payment codes for miscellaneous injectable drugs, each Medicare carrier reviews such reimbursement requests separately. Uniform national Medicare reimbursement for our injectable drug products will require a favorable National Coverage Determination for our injectable drug, which would be issued by CMS following review of an application by the manufacturer. Although they are not required to do so, private health insurers often follow the Medicare program's lead when determining whether or not to reimburse for a drug. To support our applications for reimbursement coverage with Medicare and other major third-party payers, we intend to use data from clinical trials. The lack of satisfactory reimbursement for our drug products would limit their widespread use and lower potential product revenues.

Reimbursement systems in international markets vary significantly by country and, within some countries, by region. Reimbursement approvals must be obtained on a country-by-country basis. In many foreign markets, including markets in which we anticipate selling our products, the pricing of prescription pharmaceuticals is subject to government pricing control. In these markets, once marketing approval is received, pricing negotiations could take another six to twelve months or longer. As in the United States, the lack of satisfactory reimbursement or inadequate government pricing of our products would limit their widespread use and lower potential product revenues.

Competition

The markets for therapies that treat diseases and conditions of the eye are subject to intense competition and technological change. Many companies, including major pharmaceutical companies and specialized biotechnology companies, are engaged in activities similar to ours. Such companies include Allergan, Inc., Alcon Laboratories, Inc., Bausch & Lomb Incorporated, Novartis Ophthalmics (a unit of Novartis AG), Pfizer, Inc. and Eli Lilly and Company. Many of these companies have substantially greater financial and other resources, larger research and development staffs and more

extensive marketing and manufacturing organizations than ours. Many of these companies have significant experience in preclinical testing, clinical trials and other parts of the regulatory approval process.

Should we be successful in acquiring or obtaining licenses for currently marketed ophthalmic products, we will be subject to intense competition from major pharmaceutical companies who have extensive marketing and distribution organizations and substantially greater financial resources than ours.

We are not aware of any other drug candidates in clinical trials for the treatment of vitreous hemorrhage or hyphema. Eli Lilly and Company is currently conducting clinical trials for the use of a systemic drug to treat diabetic retinopathy, and several companies are working on drugs and systems to help control diabetes and the consequences of diabetes, including diabetic retinopathy. In addition, numerous companies are working on alternate therapies for ocular inflammation and glaucoma.

Our success will depend, in part, on our ability to:

- demonstrate the safety and efficacy of our products;
- obtain regulatory approval in a timely manner;
- demonstrate potential advantages over alternate treatment methods;
- effectively market and distribute our products, either through our collaborators or by establishing and enhancing our own resources in these areas;
- obtain reimbursement coverage from insurance companies and other third-party payers;
- demonstrate cost-effectiveness; and
- obtain patent protection and effectively enforce our patent rights.

Manufacturing

Ovine hyaluronidase, the active pharmaceutical ingredient used in Vitrase®, is sourced from ovine testes and processed in several stages to produce a highly purified raw material for formulation. We have a supply agreement with Biozyme Laboratories Ltd. for current Good Manufacturing Practices ("cGMP")-grade ovine hyaluronidase for use in ophthalmic applications. The ovine hyaluronidase is lyophilized, or freeze dried, by Biozyme and delivered to our contract manufacturer for formulation and filling of dose specific vials. Vitrase® is currently required to be stored under refrigerated conditions prior to its use. We have entered into an agreement with R.P. Scherer West, Inc. to manufacture commercial quantities of Vitrase®. R.P. Scherer West is a wholly owned subsidiary of Cardinal Health. Under the terms of the agreement, Cardinal Health will manufacture, package and perform certain manufacturing quality assurance and quality control tests on the product in accordance with specifications provided by us. Currently, Biozyme and Cardinal Health are our sole sources for ovine hyaluronidase and the finished product, respectively. We are seeking additional manufacturing sources for these products.

We have supply agreements with Bausch & Lomb to manufacture commercial quantities of Istalol™ and Xibrom™. Under the terms of the agreements, Bausch & Lomb will manufacture, package and perform certain manufacturing quality assurance and quality control tests on the two products in accordance with specifications provided by us. Currently, Bausch & Lomb is our sole source for Istalol™ and Xibrom™.

Research and Development

Since our inception, we have made substantial investments in research and development. During the years ended December 31, 2003, 2002 and 2001, we spent $17.3 million, $14.8 million and $15.8 million, respectively, on research and development activities.

We plan to focus our near-term research and development efforts on the continued development of the products in our current development pipeline, which include Vitrase®, Istalol™, Xibrom™ and Caprogel®. Building on this pipeline, our goal is to continue our growth as a specialty pharmaceutical company by developing or acquiring complementary products, either already marketed or in late-stage development. Some acquired products may require additional research and development activities prior to regulatory approval and commercialization.

Patents and Proprietary Rights

Our success will depend in part on our ability to obtain patent protection for our inventions, to preserve our trade secrets and to operate without infringing the proprietary rights of third parties. Our strategy is to actively pursue patent protection in the United States and foreign jurisdictions for technology that we believe to be proprietary and that offers a potential competitive advantage for our inventions. We currently own or license 49 United States and foreign patent applications and 25 United States and foreign issued patents.

In addition to patents, we rely on trade secrets and proprietary know-how. We seek protection of these trade secrets and proprietary know-how, in part, through confidentiality and proprietary information agreements. We make efforts to require our employees, directors, consultants and advisors, outside scientific collaborators and sponsored researchers, other advisors and other individuals and entities to execute confidentiality agreements upon the start of employment, consulting or other contractual relationships with us. These agreements provide that all confidential information developed or made known to the individual or entity during the course of the relationship is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees and some other parties, the agreements provide that all inventions conceived by the individual will be our exclusive property. These agreements may not provide meaningful protection for or adequate remedies to protect our technology in the event of unauthorized use or disclosure of information. Furthermore, our trade secrets may otherwise become known to, or be independently developed by, our competitors.

We also file trademark applications to protect the names of our products. These applications may not mature to registration and may be challenged by third parties. We are pursuing trademark protection for Vitrase® in a number of different countries around the world. We have exclusively licensed the trademark Vitrase® to Allergan under our collaboration agreement.

Government Regulation

Our pharmaceutical products are subject to extensive government regulation in the United States. If we distribute our products abroad, these products will also be subject to extensive foreign government regulation. In the United States, the FDA regulates pharmaceutical products. FDA regulations govern the testing, manufacturing, advertising, promotion, labeling, sale and distribution of our products.

The FDA approval process for drugs includes:

- preclinical studies;
- submission of an investigational NDA for clinical trials;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the product;
- submission of a NDA;
- review of the NDA; and
- inspection of the facilities used in the manufacturing of the drug to assess compliance with the current Good Manufacturing Practices regulations.

The NDA includes comprehensive and complete descriptions of the preclinical testing, clinical trials, and the chemical, manufacturing and control requirements of a drug that enables the FDA to determine the drug's safety and efficacy. A NDA must be submitted by us, and filed and approved by the FDA before any of our drugs can be marketed commercially in the United States.

The FDA testing and approval process requires substantial time, effort and money. We cannot assure you that any approval will ever be granted.

Preclinical studies include laboratory evaluation of the product, as well as animal studies to assess the potential safety and effectiveness of the product. These studies must be performed according to good laboratory practices. The results of the preclinical studies, together with manufacturing information and analytical data, are submitted to the FDA as part of the Investigational New Drug Application ("IND"). Clinical trials may begin 30 days after the IND is received, unless the FDA raises concerns or questions about the conduct of the clinical trials. If concerns or questions are raised, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed.

We cannot assure you that submission of an IND will result in authorization to commence clinical trials. Nor can we assure you that if clinical trials are approved, that data will result in marketing approval. Clinical trials involve the

administration of the product that is the subject of the trial to volunteers or patients under the supervision of a qualified principal investigator. Furthermore, each clinical trial must be reviewed and approved by an independent institutional review board at each institution at which the study will be conducted. The institutional review board will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution. Also, clinical trials must be performed according to good clinical practices. Good clinical practices are enumerated in FDA regulations and guidance documents.

Clinical trials typically are conducted in three sequential phases: Phases I, II and III, with Phase IV studies conducted after approval and generally required for drugs subject to accelerated approval regulations. These phases may overlap. In Phase I clinical trials, the drug is usually tested on healthy volunteers to determine:

- safety;
- any adverse effects;
- dosage tolerance;
- absorption;
- metabolism;
- distribution;
- excretion; and
- other drug effects.

In Phase II clinical trials, the drug is usually tested on a limited number of afflicted patients to evaluate the efficacy of the drug for specific, targeted indications, determine dosage tolerance and optimal dosage, identify possible adverse effects and safety risks. In Phase III clinical trials, the drug is usually tested on a larger number of patients, in an expanded patient population and at multiple clinical sites. The FDA may require that we suspend clinical trials at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk.

In Phase IV clinical trials or other post-approval commitments, additional studies and patient follow-up are conducted to gain experience from the treatment of patients in the intended therapeutic indication. Additional studies and follow-up are also conducted to document a clinical benefit where drugs are approved under accelerated approval regulations and based on surrogate endpoints. In clinical trials, surrogate endpoints are alternative measurements of the symptoms of a disease or condition that are substituted for measurements of observable clinical symptoms. Failure to promptly conduct Phase IV clinical trials and follow-up could result in expedited withdrawal of products approved under accelerated approval regulations.

The facilities, procedures, and operations of our contract manufacturers must be determined to be adequate by the FDA before approval of product manufacturing. Manufacturing facilities are subject to inspections by the FDA for compliance with cGMP, licensing specifications, and other FDA regulations before and after a NDA has been approved. Foreign manufacturing facilities are also subject to periodic FDA inspections or inspections by foreign regulatory authorities. Among other things, the FDA may withhold approval of NDAs or other product applications of a facility if deficiencies are found at the facility. Vendors that supply us finished products or components used to manufacture, package and label products are subject to similar regulation and periodic inspections.

Following such inspections, the FDA may issue notices on Form 483 and Warning Letters that could cause us to modify certain activities identified during the inspection. A Form 483 notice is generally issued at the conclusion of a FDA inspection and lists conditions the FDA investigators believe may violate cGMP or other FDA regulations. FDA guidelines specify that a Warning Letter be issued only for violations of "regulatory significance" for which the failure to adequately and promptly achieve correction maybe expected to result in an enforcement action.

In addition, the FDA imposes a number of complex regulatory requirements on entities that advertise and promote pharmaceuticals, including, but not limited to, standards and regulations for direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet.

Failure to comply with FDA and other governmental regulations can result in fines, unanticipated compliance expenditures, recall or seizure of products, total or partial suspension of production and/or distribution, suspension of the FDA's review of NDAs, injunctions and criminal prosecution. Any of these actions could have a material adverse effect on us.

Food and Drug Administration Modernization Act of 1997

The Food and Drug Administration Modernization Act of 1997 was enacted, in part, to ensure the availability of safe and effective drugs, biologics and medical devices by expediting the FDA review process for new products. The Modernization Act establishes a statutory program for the approval of fast-track products. The fast-track provisions essentially codify the FDA's accelerated approval regulations for drugs and biologics. A fast-track product is defined as a new drug or biologic intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for this condition. Under the new fast-track program, the sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a fast-track product at any time during the clinical development of the product. The Modernization Act specifies that the FDA must determine if the product qualifies for fast-track designation within 60 days of receipt of the sponsor's request. Fast- track designated products may qualify for accelerated approval and priority review, or review within six months. Accelerated approval will be subject to:

- post-approval studies and follow-up to validate the surrogate endpoint or confirm the effect on the clinical endpoint; and
- prior review of all promotional materials.

If a preliminary review of the clinical data suggests that the product is effective, the FDA may initiate review of sections of an application for fast-track designation for a product before the application is complete. This rolling review is available if the applicant provides a schedule for submission of remaining information and pays applicable user fees. However, the time period specified in the Prescription Drug User Fees Act of 1992, which governs the time period goals the FDA has committed for reviewing an application, does not begin until the complete application is submitted.

In October 1998, the FDA granted our application for fast-track designation for Vitrase® for the treatment of vitreous hemorrhage. During 2002 we submitted three sections of the Vitrase® NDA as they were completed. The pre-clinical pharmacology and toxicology section was submitted in January 2002. The clinical section and the CMC section were submitted in October 2002. The FDA accepted those sections of the Vitrase® NDA for review in December 2002, along with the pre-clinical pharmacology and toxicology section that was submitted in January 2002. On April 3, 2003, the FDA issued an approvable letter in which the FDA cited issues primarily related to the sufficiency of the efficacy data submitted with the NDA for Vitrase®. We have submitted information to the FDA in response to its non-clinical comments contained in the approvable letter and are continuing to assess and discuss with the agency the clinical issues raised in the approvable letter. Based upon these discussions, we will determine the next appropriate steps in the approval process of Vitrase® for the treatment of vitreous hemorrhage.

In August 2003, we submitted to the FDA a second NDA for Vitrase® for use as a spreading agent to facilitate the dispersion and absorption of other drugs. The FDA granted "priority review" status for this NDA in August 2003 and accepted the NDA for filing and review in October 2003. In February 2004, the FDA notified ISTA that it was extending the PDUFA action date 90 days to May 5, 2004. The product submitted in the second NDA is the same formulation as the product submitted in the original Vitrase® NDA for the treatment of vitreous hemorrhage. The dose used as a spreading agent is different than the dose used for injection into the posterior region of the eye. With respect to the second Vitrase® NDA, we are pursuing the development of additional package configurations for different doses of the product to facilitate product utilization, improve profit margins and aid in obtaining appropriate third-party reimbursement. Upon approval of the second Vitrase® NDA, we intend to submit supplemental filings with the FDA with respect to such additional package configurations.

One of our product candidates, Caprogel®, for the treatment of hyphema, has been designated by the FDA as an orphan drug. An orphan drug is defined in the 1984 amendments of the Orphan Drug Act as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States. The Orphan Drug Act has numerous incentives including:

- seven years of exclusive marketing upon FDA approval;
- tax credit for clinical research expense;
- grant support for investigation of rare disease treatments; and
- user fee waiver.

International

For marketing outside the United States, we also are subject to foreign regulatory requirements governing human clinical trials and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product approval, pricing and reimbursement vary widely from country to country. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained before manufacturing or marketing the product in those countries. The approval process varies from country to country and the time required for such approvals may differ substantially from that required for FDA approval. We cannot assure you that clinical trials conducted in one country will be accepted by other countries or that approval in one country will result in approval in any other country. For clinical trials conducted outside the United States, the clinical stages are generally comparable to the phases of clinical development established by the FDA.

Human Resources

As of March 17, 2004, we had 47 full-time employees. Approximately 33 of our employees are involved in research and clinical development activities. Five of our employees hold Ph.D. degrees and ten other employees hold other advanced degrees. Our employees do not have a collective bargaining agreement. We consider our relations with our employees to be good.

General Information

We incorporated in California in February 1992 as Advanced Corneal Systems, Inc. In March 2000, we changed our name to ISTA Pharmaceuticals, Inc., and we reincorporated in Delaware in August 2000. Our corporate headquarters and principal research laboratories are located at 15279 Alton Parkway, Suite 100, Irvine, CA 92618, and our telephone number is (949) 788-6000. Vitrase®, Istalol™, Xibrom™, Caprogel®, ISTA, ISTA Pharmaceuticals and the ISTA logo are our trademarks.

We make our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to these reports available on our website, at http://www.istavision.com, free of charge as soon as practicable after filing with the SEC. All such reports are also available free of charge via EDGAR through the SEC website at www.sec.gov. In addition, the public may read and copy materials filed by ISTA with the SEC at the SEC's public reference room located at 450 Fifth St., N.W., Washington, D.C., 20549. Information regarding operation of the SEC's public reference room can be obtained by calling the SEC at 1-800-SEC-0330.

RISK FACTORS

In addition to other information included in this report, the following factors should be considered in evaluating our business and future prospects:

Risks Related to Our Business

If we do not receive and maintain regulatory approvals for our product candidates, we, or our marketing partners, will not be able to commercialize our products, which would substantially impair our ability to generate revenues and materially harm our business and financial condition.

None of our product candidates has received regulatory approval from the FDA. Approval from the FDA is necessary to manufacture and market pharmaceutical products in the United States. Many other countries including major European countries and Japan have similar requirements.

The NDA process is extensive, time-consuming and costly, and there is no guarantee that the FDA will approve NDAs of any of our product candidates, or that the timing of any such approval will be appropriate for our product launch schedule and other business priorities, which are subject to change. We have submitted NDAs which are currently pending before the FDA, two for Vitrase®, for the treatment of vitreous hemorrhage and for use as a spreading agent, respectively, and one for Istalol™. Moreover, we depend on the assistance of Senju for obtaining regulatory approval for Istalol™.

Although we have received an approvable letter from the FDA with respect to our NDA for Vitrase® for the treatment of vitreous hemorrhage, the FDA has requested additional analysis of the existing data and an additional confirmatory clinical study based upon that analysis. There can be no assurances that the FDA will approve this NDA for Vitrase®, even if we decide to and are successfully able to undertake the further analysis and clinical testing requested by the FDA.

Although we have received "priority review" status on our second NDA for Vitrase® for its use as a spreading agent, there can be no assurances that the FDA will approve this NDA. Even if the FDA ultimately does approve this NDA, the timing of, or conditions imposed by the FDA on any such approval might not be appropriate for our marketing, product development and business priorities or those of Allergan, our marketing partner for uses in the posterior region of the eye.

The FDA has also issued an approvable letter with respect to the Istalol™ NDA, citing issues related to manufacturing methods and controls. While we believe these issues are addressable, there can be no assurance that the FDA will approve the NDA for Istalol™, or that the timing of any such approval would be appropriate in view of our changing business objectives and priorities.

Clinical testing of pharmaceutical products is also a long, expensive and uncertain process. Even if initial results of preclinical studies or clinical trial results are positive, we may obtain different results in later stages of drug development, including failure to show desired safety and efficacy. We completed our Phase III studies of Xibrom™, a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation, and announced initial results of our clinical studies in March 2004. Based on the initial results of our Phase III studies, we anticipate submitting a NDA for Xibrom™ in the second quarter of 2004.

The clinical trials of any of our product candidates could be unsuccessful, which would prevent us from obtaining regulatory approval and commercializing the product.

FDA approval can be delayed, limited or not granted for many reasons, including, among others:

- FDA officials may not find a product candidate safe or effective to merit an approval;
- FDA officials may not find that the data from preclinical testing and clinical trials justifies approval, or they may require additional studies that would make it commercially unattractive to continue pursuit of approval;
- the FDA might not approve our manufacturing processes or facilities, or the processes or facilities of our contract manufacturers or raw material suppliers;
- the FDA may change its approval policies or adopt new regulations; and
- the FDA may approve a product candidate for indications that are narrow or under conditions that place our product at a competitive disadvantage, which may limit our sales and marketing activities or otherwise adversely impact the commercial potential of a product.

If the FDA does not approve our product candidates in a timely fashion on commercially viable terms or we terminate development of any of our product candidates due to difficulties or delays encountered in the regulatory approval process, it will have a material adverse impact on our business and we will be dependent on the development of our other product candidates and/or our ability to successfully acquire other products and technologies.

In addition, we intend to market certain of our products, and perhaps have certain of our products manufactured, in foreign countries. The process of obtaining approvals in foreign countries is subject to delay and failure for similar reasons.

Even if we obtain FDA approval of the Vitrase® NDA for use as a spreading agent, our ability to commercialize Vitrase® for such use is dependent upon the terms of our collaboration with Allergan.

We have entered into a collaboration with Allergan, Inc. relating to Vitrase® for ophthalmic uses for the posterior region of the eye. If we obtain regulatory approval for Vitrase® for any such uses in the United States and Europe, we will be dependent on Allergan for the commercialization of Vitrase® for such uses in these markets. We are currently in discussions with Allergan regarding marketing and other strategies in the event the FDA approves our NDA for Vitrase® for use as a spreading agent. Allergan has informed us of its position that we need its authorization pursuant to our collaboration to market Vitrase® on our own as a spreading agent, which Allergan asserts has not been provided. In addition, Allergan may be unwilling to pursue the marketing and commercialization of Vitrase® with any final approved labeling that does not meet its satisfaction. Any dispute regarding our rights or Allergan's rights under our collaboration or otherwise would be costly, time-consuming and potentially delay or possibly prevent the launch of any approved Vitrase® product.

If our product candidates are approved by the FDA but do not gain market acceptance, our business will suffer because we might not be able to fund future operations.

A number of factors may affect the market acceptance of Vitrase®, Istalol™, Xibrom™, Caprogel® or any other products we develop or acquire in the future, including, among others:

- the price of our products relative to other therapies for the same or similar treatments;
- the perception by patients, physicians and other members of the health care community of the effectiveness and safety of our products for their prescribed treatments;
- our ability to fund our sales and marketing efforts; and
- the effectiveness of our sales and marketing efforts.

In addition, our ability to market and promote our products will be restricted to the labels approved by the FDA. If the approved labels are restrictive, our sales and marketing efforts and market acceptance and the commercial potential of our products may be negatively affected. For example, should the market not widely accept Vitrase® for usage based on the label of the second NDA, we may have to await approval of additional indications in order to reach the full market potential for this drug.

If our products do not gain market acceptance we may not be able to fund future operations, including the development or acquisition of new product candidates and/or our sales and marketing efforts for our approved products, which would cause our business to suffer.

If we are unable to sufficiently develop our sales, marketing and distribution capabilities and/or enter into agreements with third parties to perform these functions, we will not be able to commercialize products.

We currently are in the process of developing our sales, marketing and distribution capabilities. However, our current capabilities in these areas are limited. In order to commercialize any products successfully, we must internally develop substantial sales, marketing and distribution capabilities, and/or establish collaborations or other arrangements with third parties to perform these services. We do not have extensive experience in these areas, and we may not be able to establish adequate in-house sales, marketing and distribution capabilities or engage and effectively manage relationships with third parties to perform any or all of such services. For example, although we intend to develop our own sales and marketing capabilities (either in-house and/or through contractual arrangements with third parties) with respect to our other product candidates, we intend to rely on the sales and marketing capabilities of Allergan in the United States and Europe and Otsuka Pharmaceuticals, Co. Ltd. in Japan, respectively, to market Vitrase® for ophthalmic uses for the posterior region of the eye. To the extent that we enter into co-promotion, licensing or other third party arrangements, our product revenues and returns are likely to be lower than if we directly marketed and sold our products, and any revenues we receive will depend upon the efforts of third parties, whose efforts may not be successful.

We have not generated any revenue from product sales to date, we have a history of net losses and negative cash flow, and we may never achieve or maintain profitability.

We have not generated any revenue from product sales to date, and we may never generate revenues from product sales in the future. Even if we do achieve significant revenues from product sales, we expect to incur significant operating losses over the next several years. We have never been profitable, and we might never become profitable. As of December 31, 2003, our accumulated deficit was $147.6 million, including a net loss of approximately $25.2 million for the year ended December 31, 2003. As of December 31, 2003, we had approximately $48.5 million in cash and short-term investments and working capital of $44.2 million. We believe our current cash and cash equivalents on hand will be sufficient to finance anticipated capital and operating requirements for at least the next twelve months. If we engage in acquisitions of companies, products, or technology in order to execute our business strategy, we may need to raise additional capital. We may be required to raise additional capital in the future through collaborative agreements, private investment in public equity financings, and various other public or private equity or debt financings. If we are required to raise additional capital in the future there can be no assurance that the additional financing will be available on favorable terms, or at all.

We may be unable to execute our strategic plan to transition to a specialty pharmaceutical company, which could have a material adverse impact on our business and financial condition.

Our strategy to transition to a specialty pharmaceutical company will be dependent upon our ability to gain regulatory approval and market acceptance for our existing late-stage ophthalmic product candidates, build a commercial infrastructure to support multiple ophthalmic product launches, conduct business development efforts to further expand our late-stage product pipeline, and pursue opportunistic acquisitions of marketed products.

We have limited sales, marketing and distribution capabilities to support the marketing of any products, and we do not have experience in managing third-party manufacturers of any products in commercial quantities. In addition, if we acquire or obtain licenses for late-stage development products, our ability to successfully commercialize such products will also be dependent on our ability to successfully complete development of such products, including obtaining the necessary regulatory approvals. For example, we have obtained licenses for U.S. marketing rights to Istalol™ and Xibrom™ from Senju, and we have obtained a license for worldwide rights to Caprogel® from the Eastern Virginia Medical School. Senju is responsible for the development of Istalol™, including obtaining the necessary regulatory approvals in the United States. We are responsible for the development of Xibrom™ and Caprogel®.

We may not be able to identify any product acquisition opportunities or be successful in negotiating favorable terms for any such product acquisitions. Should we be successful in acquiring or licensing any products, we will need to establish and enhance our sales, marketing, distribution and manufacturing capabilities, each of which will require substantial financial and management resources. Our failure to establish effective sales, marketing, distribution and manufacturing capabilities on a timely basis would adversely affect our ability to commercialize our products, including any acquired products. If we are unable to execute our strategic plan to transition to a specialty pharmaceutical company on a timely basis, our ability to generate revenues would be substantially impaired which would materially harm our business and financial condition.

If we have problems with our contract manufacturers, our product development and commercialization efforts could be delayed or stopped.

We have entered into a master services agreement with R.P. Scherer West, Inc. (which has been subsequently acquired by Cardinal Health, Inc.), for the manufacture of commercial quantities, if approved, of Vitrase®. We also intend to use a contract manufacturer to assist us in the development and manufacture of the new package configurations of Vitrase®, if approved. We have also entered into a manufacturing services agreement with Bausch & Lomb Incorporated for the manufacture of commercial quantities, if approved, of Istalol™ and Xibrom™. To date, we have needed these products only in amounts sufficient for clinical trials. Before any contract manufacturer can produce commercial quantities of a product, we must demonstrate to the FDA's satisfaction that the product source for commercial quantities is substantially equivalent to the supply of the product used in our clinical trials. Such demonstration may include the requirement to conduct additional clinical trials. In December 2003, we submitted documents to the FDA seeking to qualify Bausch & Lomb as an alternate manufacturer of Istalol™. In addition, the manufacturing facilities of all of our contract manufacturers must comply with current Good Manufacturing Practice ("cGMP") regulations, which the FDA strictly enforces. Moreover, the facilities of the contract manufacturer must undergo and pass pre-approval inspections by the FDA before any of our products can be approved for commercial manufacture. We cannot assure you that Cardinal Health, Bausch & Lomb, or any other manufacturer we may contract with in the future will be able, as applicable, to develop processes necessary to produce substantially equivalent product or that regulatory authorities will approve them as a manufacturer. Failure to develop necessary production processes or receive regulatory approval of our manufacturers could delay or stop our efforts to develop and commercialize our product candidates.

Our marketing partners may terminate, or fail to perform their duties under, our agreements, in which case our ability to commercialize our products may be significantly impaired.

We have entered into collaborations with Allergan and Otsuka Pharmaceuticals relating to Vitrase® for ophthalmic uses for the posterior region of the eye, and with Senju relating to Istalol™ and Xibrom™. If we obtain regulatory approval for Vitrase® for any such uses in the United States and Europe, we will be dependent on Allergan for the commercialization of Vitrase® for any such uses in these markets. We depend on Otsuka for obtaining regulatory approval of Vitrase® for any such uses in Japan, and if such approval is obtained, we will be dependent upon Otsuka for the commercialization of Vitrase® for such approved uses in Japan. We will also be dependent on Senju for obtaining regulatory approval for Istalol™ in the United States. The amount and timing of resources that Allergan, Otsuka, and Senju dedicate to our collaborations is not within our control. Accordingly, any breach or termination of our agreements by, or disagreements with, these collaborators could delay or stop the development and/or commercialization of our product candidates, or adversely impact our receipt of milestone payments, profit splits, royalties, and other consideration from these collaborations. Our collaborative partners may change their strategic focus, terminate our agreements on relatively short notice, or pursue alternative technologies. Although our agreements with Allergan, Otsuka and Senju contain reciprocal terms providing that neither we nor they may develop products that directly compete in the same form with the products involved in the collaboration, there can be no assurances that our collaborators will not develop competing products in different forms or products that compete indirectly with our products. Accordingly, unfavorable developments relating to our strategic partners could have a significant adverse effect on us and our financial condition.

If we have problems with our sole source suppliers, our product development and commercialization efforts for our product candidates could be delayed or stopped.

Some materials used in our products are currently obtained from a single source. Biozyme Laboratories, Ltd. is currently our only source for highly purified ovine hyaluronidase, which is the active ingredient in Vitrase®. We are currently renegotiating our agreement with Biozyme. If we are unable to renegotiate our agreement on terms acceptable to us, we may be required to obtain ovine hyaluronidase from a third party supplier, if available. If approved, commercial quantities of Vitrase® will be supplied by Cardinal Health as the sole source. Istalol™, if approved, will be supplied by Akorn Laboratories and/or Bausch & Lomb. Xibrom™, if approved, will be supplied by a single source, Bausch & Lomb.

We have not established and may not be able to establish arrangements with additional suppliers for these ingredients or products. Difficulties in our relationship with our suppliers or delays or interruptions in such suppliers' supply of our requirements could limit or stop our ability to provide sufficient quantities of our products, on a timely basis, for clinical trials and, if our products are approved, could limit or stop commercial sales, which would have a material adverse effect on our business and financial condition. While we are currently pursuing additional sources for these products and materials, our success in establishing such additional supply arrangements cannot be assured.

We depend on our Chief Executive Officer, Vicente Anido, Jr., Ph.D., and other key personnel, to execute our strategic plan to transition to a specialty pharmaceutical company.

Our success largely depends on the skills, experience and efforts of our key personnel, including Chief Executive Officer, Vicente Anido, Jr., Ph.D. We have entered into a written employment agreement with Dr. Anido that can be terminated at any time by us or by Dr. Anido. In the event Dr. Anido's employment is terminated, other than for cause or voluntarily by Dr. Anido, Dr. Anido will receive nine months of salary as severance compensation. In the event Dr. Anido's employment is terminated after a change of control (such as a merger where we are bought by another entity, or a sale of substantially all of our assets), other than for cause or voluntarily by Dr. Anido, then Dr. Anido's stock options will immediately vest and become exercisable in full, and Dr. Anido will receive twenty-four months of salary as severance compensation. We do not maintain "key person" life insurance policies covering Dr. Anido. The loss of Dr. Anido, or our failure to retain other key personnel, would jeopardize our ability to execute our strategic plan and materially harm our business.

Risks Related to Our Industry

Compliance with the extensive government regulations to which we are subject is expensive and time consuming, and may result in the delay or cancellation of product sales, introductions or modifications.

Extensive industry regulation has had, and will continue to have, a significant impact on our business. All pharmaceutical companies, including us, are subject to extensive, complex, costly and evolving regulation by the federal government, principally the FDA and to a lesser extent by the U.S. Drug Enforcement Administration ("DEA"), and foreign and state government agencies. The Federal Food, Drug and Cosmetic Act, the Controlled Substances Act and other domestic and foreign statutes and regulations govern or influence the testing, manufacturing, packing, labeling, storing, record

keeping, safety, approval, advertising, promotion, sale and distribution of our products. Under certain of these regulations, we and our contract suppliers and manufacturers are subject to periodic inspection of our or their respective facilities, procedures and operations and/or the testing of our products by the FDA, the DEA and other authorities, which conduct periodic inspections to confirm that we and our contract suppliers and manufacturers are in compliance with all applicable regulations. The FDA also conducts pre-approval and post-approval reviews and plant inspections to determine whether our systems, or our contract suppliers' and manufacturers' processes, are in compliance with cGMP and other FDA regulations.

In addition, the FDA imposes a number of complex regulatory requirements on entities that advertise and promote pharmaceuticals, including, but not limited to, standards and regulations for direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet.

We are dependent on receiving FDA and other governmental approvals prior to manufacturing, marketing and shipping our products. Consequently, there is always a risk that the FDA or other applicable governmental authorities will not approve our products, or will take post-approval action limiting or revoking our ability to sell our products, or that the rate, timing and cost of such approvals will adversely affect our product introduction plans or results of operations.

Our suppliers and manufacturers are subject to regulation by the FDA and other agencies, and if they do not meet their commitments, we would have to find substitute suppliers or manufacturers, which could delay the supply of our products to market.

Regulatory requirements applicable to pharmaceutical products make the substitution of suppliers and manufacturers costly and time consuming. We have no internal manufacturing capabilities and are, and expect to be in the future, entirely dependent on contract manufacturers and suppliers for the manufacture of our products and for their active and other ingredients. The disqualification of these suppliers through their failure to comply with regulatory requirements could negatively impact our business because the delays and costs in obtaining and qualifying alternate suppliers (if such alternative suppliers are available, which we cannot assure) could delay clinical trials or otherwise inhibit our ability to bring approved products to market, which would have a material adverse affect on our business and financial condition.

We may be required to initiate or defend against legal proceedings related to intellectual property rights, which may result in substantial expense, delay and/or cessation of our development and commercialization of our products.

We rely on patents to protect our intellectual property rights. The strength of this protection, however, is uncertain. For example, it is not certain that:

- our patents and pending patent applications cover products and/or technology that we invented first;
- we were the first to file patent applications for these inventions;
- others will not independently develop similar or alternative technologies or duplicate our technologies;
- any of our pending patent applications will result in issued patents; and
- any of our issued patents, or patent pending applications that result in issued patents, will be held valid and infringed in the event the patents are asserted against others.

We currently own or license 25 U.S. and foreign patents and 49 U.S. and foreign pending patent applications. There can be no assurance that our existing patents, or any patents issued to us as a result of such applications, will provide a basis for commercially viable products, will provide us with any competitive advantages, or will not face third-party challenges or be the subject of further proceedings limiting their scope or enforceability. We may become involved in interference proceedings in the U.S. Patent and Trademark Office to determine the priority of our inventions. In addition, costly litigation could be necessary to protect our patent position. We license patents held by the Eastern Virginia Medical School (for Caprogel®) and Senju (for Istalol™ and Xibrom™). Some of these license agreements do not permit us to control the prosecution, maintenance, protection and defense of such patents. If the licensor chooses not to protect its own patent rights, we may not be able to take actions to secure our related product marketing rights. In addition, if such patent licenses are terminated before the expiration of the licensed patents, we may no longer be able to continue to manufacture and sell such products as may be covered by the patents.

We also rely on trademarks to protect the names of our products. These trademarks may be challenged by others. If we enforce our trademarks against third parties, such enforcement proceedings may be expensive. We have exclusively licensed the trademark Vitrase® to Allergan under our collaboration agreement. Some of our other trademarks, including Caprogel™ and Xibrom™, are owned by or assignable to our licensors Eastern Virginia Medical School and Senju, and upon expiration or termination of the license agreements, we may no longer be able to use these trademarks.

We also rely on trade secrets, unpatented proprietary know-how and continuing technological innovation that we seek to protect with confidentiality agreements with employees, consultants and others with whom we discuss our business. Disputes may arise concerning the ownership of intellectual property or the applicability or enforceability of these agreements, and we might not be able to resolve these disputes in our favor.

In addition to protecting our own intellectual property rights, third parties may assert patent, trademark or copyright infringement or other intellectual property claims against us based on what they believe are their own intellectual property rights. We may be required to pay substantial damages, including but not limited to treble damages, for past infringement if it is ultimately determined that our products infringe a third party's intellectual property rights. Even if infringement claims against us are without merit, defending a lawsuit takes significant time, may be expensive and may divert management's attention from other business concerns. Further, we may be stopped from developing, manufacturing or selling our products until we obtain a license from the owner of the relevant technology or other intellectual property rights. If such a license is available at all, it may require us to pay substantial royalties or other fees.

If third-party reimbursement is not available, our products may not be accepted in the market.

Our ability to earn sufficient returns on our products will depend in part on the extent to which reimbursement for our products and related treatments will be available from government health administration authorities, private health insurers, managed care organizations and other healthcare providers.

Third-party payers are increasingly attempting to limit both the coverage and the level of reimbursement of new drug products to contain costs. Consequently, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. If we succeed in bringing one or more of our product candidates to market, third-party payers may not establish adequate levels of reimbursement for our products, which could limit their market acceptance and result in a material adverse effect on our financial condition.

We face intense competition and rapid technological change that could result in the development of products by others that are superior to the products we are developing.

We have numerous competitors in the United States and abroad, including, among others, major pharmaceutical and specialized biotechnology firms, universities and other research institutions that may be developing competing products. Such competitors may include Allergan, Alcon Laboratories, Inc., Bausch & Lomb, Novartis Ophthalmics (a unit of Novartis AG), Pfizer and Eli Lilly and Company. These competitors may develop technologies and products that are more effective or less costly than our current or future product candidates or that could render our technologies and product candidates obsolete or noncompetitive. Many of these competitors have substantially more resources and product development, manufacturing and marketing experience and capabilities than we do. In addition, many of our competitors have significantly greater experience than we do in undertaking preclinical testing and clinical trials of pharmaceutical product candidates and obtaining FDA and other regulatory approvals of products and therapies for use in healthcare.

We are exposed to product liability claims, and insurance against these claims may not be available to us on reasonable terms or at all.

We currently maintain clinical trial liability insurance with per occurrence and aggregate coverage limits of $5 million. The coverage limits of our insurance policies may be inadequate to protect us from any liabilities we might incur in connection with clinical trials or the sale of our products. Product liability insurance is expensive and in the future may not be available on commercially acceptable terms, or at all. A successful claim or claims brought against us in excess of our insurance coverage could materially harm our business and financial condition.

Risks Related to Our Stock

Our stock price is subject to significant volatility.

Since 2001 until the present, the daily closing price per share of our common stock has ranged from a high of $133.75 per share to a low of $2.60 per share (as adjusted for the 1-for-10 reverse stock split effected November 2002). Our stock price has been and may continue to be subject to significant volatility. The following factors, in addition to other risks and uncertainties described in this section and elsewhere in this prospectus, may cause the market price of our common stock to fall:

- the scope, outcome and timeliness of any governmental, court or other regulatory action that may involve us (including, without limitation, the scope, outcome or timeliness of any inspection or other action of the FDA);

- the availability to us, on commercially reasonable terms or at all, of third-party sourced products and materials;
- developments concerning proprietary rights, including the ability of third parties to assert patents or other intellectual property rights against us which, among other things, could cause a delay or disruption in the development, manufacture, marketing or sale of our products;
- competitors' publicity regarding actual or potential products under development or new commercial products;
- period-to-period fluctuations in our financial results;
- public concern as to the safety of new technologies;
- future sales of debt or equity securities by us;
- sales of our common stock by our directors, officers or significant shareholders;
- comments made by securities analysts; or
- economic and other external factors, including disasters and other crises.

We participate in a highly dynamic industry, which often results in significant volatility in the market price of our common stock irrespective of company performance. Fluctuations in the price of our common stock may be exacerbated by conditions in the healthcare and technology industry segments or conditions in the financial markets generally.

Trading in our stock over the last 12 months has been limited, so investors may not be able to sell as much stock as they want at prevailing prices.

The average daily trading volume in our common stock for the twelve-month period ending March 17, 2004 was approximately 20,778 shares, and the average daily number of transactions was approximately 82 for the same period. If limited trading in our stock continues, it may be difficult for investors to sell their shares in the public market at any given time at prevailing prices.

Future sales of shares of our common stock may negatively affect our stock price.

As a result of our bridge financing in September 2002, our PIPE financing transaction in November 2002, and our follow-on public offering in November 2003, we issued approximately 15.6 million shares of our common stock. The shares of common stock issued in connection with these transactions represents approximately 89% of our common stock as of March 17, 2004. In connection with our bridge financing and our PIPE financing transaction, we also issued warrants exercisable for the purchase of up to an aggregate of 1,842,104 shares of our common stock based upon a purchase price of $3.80 per share. We filed a registration statement on Form S-3 (Registration No. 333-103820), which was declared effective on June 6, 2003, to cover sales of the shares issued to the PIPE investors and issuable to the PIPE and bridge investors upon conversion of the warrants. The exercise of these warrants could result in significant dilution to our shareholders at the time of exercise. We also filed a registration statement on Form S-2 (Registration No. 333-109576) in connection with our follow-on public offering, which was declared effective on November 12, 2003, to cover sales of the shares issued the investors.

In the future, we may issue additional shares of common stock or other equity securities, including but not limited to options, warrants or other derivative securities convertible into our common stock, which could result in significant dilution to our shareholders.

Concentration of ownership could delay or prevent a change in control or otherwise influence or control most matters submitted to our stockholders.

Our directors, officers, and principal stockholders together control approximately 64.3% of our voting securities, a concentration of ownership that could delay or prevent a change in control. Our executive officers and directors beneficially own approximately 3.9% of our voting securities and our 5% or greater stockholders beneficially own approximately 60.4% of our voting securities. These stockholders, if acting together, would be able to influence and possibly control most matters submitted for approval by our stockholders, including the election of directors, delaying or preventing a change of control, and the consideration of transactions in which stockholders might otherwise receive a premium for their shares over then-current market prices.

Our shareholder rights plan, provisions in our charter documents, and Delaware law may inhibit a takeover of us, which could limit the price investors might be willing to pay in the future for our common stock, and could entrench management.

We have a shareholder rights plan that may have the effect of discouraging unsolicited takeover proposals, thereby entrenching current management and possibly depressing the market price of our common stock. The rights issued under the shareholder rights plan would cause substantial dilution to a person or group that attempts to acquire us on terms not approved in advance by our board of directors. In addition, our charter and bylaws contain provisions that may discourage unsolicited takeover proposals that stockholders may consider to be in their best interests. These provisions include:

- a classified board of directors;
- the ability of the board of directors to designate the terms of and issue new series of preferred stock;
- advance notice requirements for nominations for election to the board of directors; and
- special voting requirements for the amendment of our charter and bylaws.

We are also subject to anti-takeover provisions under Delaware law, each of which could delay or prevent a change of control. Together these provisions and the shareholder rights plan may make more difficult the removal of management and may discourage transactions that otherwise could involve payment of a premium over prevailing market prices for common stock.

We do not anticipate declaring any cash dividends on our common stock.

We have never declared or paid cash dividends on our common stock and do not plan to pay any cash dividends in the near future. Our current policy is to retain all funds and any earnings for use in the operation and expansion of our business.

Item 2: Properties

We currently lease two facilities, which approximate 19,000 square feet of laboratory and office space in Irvine, California. The current term of the first lease expires September 2004. The current term of our second lease expires June 2005. We believe that these two facilities are adequate for our immediate needs. Additional space will be required, however, as we expand our research and clinical development, manufacturing and selling and marketing activities. We do not foresee any significant difficulties in obtaining any required additional facilities close to our current facility.

Item 3: Legal Proceedings

From time to time, we may be involved in litigation relating to claims arising out of our operations in the normal course of business. We currently are not a party to any legal proceedings, the adverse outcome of which, in management's opinion, individually or in the aggregate, would have a material adverse effect on our results of operations or financial position.

Item 4: Submission of Matters to a Vote of Security Holders

No matters were voted upon during the fourth quarter of 2003.

PART II

Item 5: Market for Registrant's Common Equity and Related Stockholder Matters

Price Range of Common Stock

Our common stock began trading on the Nasdaq National Market under the symbol "ISTA" on August 21, 2000. Prior to this date, there was no public market for our common stock. Our common stock was affected by a 1-for-10 reverse stock split, which became effective at the close of trading on November 13, 2002. The following table presents high and low closing prices of our common stock, on a post split basis, as reported on the Nasdaq National Market, for the periods indicated since our initial public offering:

2002	High	Low
First quarter	$ 70.90	$ 8.30
Second quarter	13.00	6.50
Third quarter	9.00	2.60
Fourth quarter	5.10	3.00

2003	High	Low
First quarter	$ 8.24	$ 3.10
Second quarter	6.83	4.05
Third quarter	8.35	6.01
Fourth quarte	12.00	7.65

2004	High	Low
First quarter (through March 17, 2004)	$ 12.62	$ 9.15

Holders of Common Stock

As of March 17, 2004, there were approximately 208 stockholders of record of our common stock based upon the records of our transfer agent which do not include beneficial owners of common stock whose shares are held in the names of various securities brokers, dealers and registered clearing agencies.

Dividend Policy

We have never declared or paid any cash dividends on our common stock and do not intend to pay any cash dividends on our common stock in the foreseeable future.

Item 6: Selected Financial Data

The following selected financial data are derived from our consolidated financial statements. The data should be read in conjunction with our consolidated financial statements, related notes, and other financial information included herein.

	Year Ended December 31, (in thousands, except per share data)				
	2003	2002	2001	2000	1999
Consolidated Statement of Operations Data:					
Revenues	$ 278	$ 278	$ —	$ —	$ —
Costs and expenses:					
Research and development	17,250	14,751	15,770	16,200	11,062
Selling, general and administrative	8,635	8,224	7,538	6,455	3,240
Total costs and expenses	25,885	22,975	23,308	22,655	14,302
Loss from operations	(25,607)	(22,697)	(23,308)	(22,655)	(14,302)
Interest income	372	213	826	848	69
Interest expense	(10)	(473)	(25)	(50)	(51)
Net loss	(25,245)	(22,957)	(22,507)	(21,857)	(14,284)
Deemed dividend to preferred stockholders	—	—	—	(19,245)	—
Net loss attributable to common stockholders	$ (25,245)	$ (22,957)	$ (22,507)	$ (41,102)	$ (14,284)
Net loss per common share, basic and diluted(1)	$ (1.83)	$ (7.53)	$ (14.43)	$ (60.13)	$ (95.23)
Shares used in computing net loss per share, basic and diluted(1)	13,803	3,049	1,559	684	150

(1) As discussed in the Notes to the Consolidated Financial Statements, in November 2002 we completed a 1-for-10 reverse stock split to the then outstanding common stock. All historical common shares and per share data have been adjusted for the reverse stock split. Additionally, in November 2002, we consummated a private investment in public

equity transaction, which resulted in the issuance of 10,526,306 shares of common stock and in November 2003, we completed a follow-on public offering, which resulted in the issuance of 4,000,000 shares of common stock.

	As of December 31, (in thousands, except per share data)				
	2003	2002	2001	2000	1999
Consolidated Balance Sheet Data:					
Cash and cash equivalents and short-term investments	$ 48,463	$ 35,712	$ 15,602	$ 25,729	$ 709
Working capital (deficit)	44,193	33,046	12,079	23,386	(4,993)
Total assets	50,182	37,135	16,956	28,021	3,020
License fee received from Visionex	—	—	—	—	5,000
Deferred revenue	4,444	4,722	5,000	—	—
Other long-term obligations	9	10	2	12	38
Deficit accumulated during the development stage	(147,639)	(122,394)	(99,437)	(76,930)	(35,828)
Total stockholders' equity (deficit)	40,424	29,228	7,940	24,564	(8,656)

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

This Annual Report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Securities Litigation Act of 1995 and concern matters that involve risks and uncertainties that could cause actual results to differ materially from those projected in the forward-looking statements. Discussions containing forward-looking statements may be found in the material set forth under "Business," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and in other sections of this Form 10-K. Words such as "may," "will," "should," "could," "expect," "plan," "anticipate," "believe," "estimate," "predict," "potential," "continue" or similar words are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Although we believe that our opinions and expectations reflected in the forward-looking statements are reasonable as of the date of this Report, we cannot guarantee future results, levels of activity, performance or achievements, and our actual results may differ substantially from the views and expectations set forth in this Report. We expressly disclaim any intent or obligation to update any forward-looking statements after the date hereof to conform such statements to actual results or to changes in our opinions or expectations. Readers are urged to carefully review and consider the various disclosures made by us, which attempt to advise interested parties of the risks, uncertainties, and other factors that affect our business, set forth in detail in Item 1 of Part I, "Business-Risk Factors."

The following discussion and analysis should be read in conjunction with our consolidated financial statements and the notes to those statements filed as part of this Form 10-K.

Overview

We are an emerging specialty pharmaceutical company focused on the development and commercialization of unique and uniquely improved products for serious diseases and conditions of the eye. Since our inception, we have devoted our resources primarily to fund research and development programs and late-stage product acquisitions. In December 2001, we announced our strategic plan to transition from a development-stage organization to a specialty pharmaceutical company with a primary focus on ophthalmology.

In order to advance our strategic plan, we are pursuing the development of several products, including Vitrase® (ovine hyaluronidase) and Istalol™ (timolol), which are in the later stages of review by the FDA. There can be no assurances that either Vitrase® or Istalol™ will receive final FDA approval. Even if we receive FDA approval of the Vitrase® NDA for use as a spreading agent, the launch of the product may require FDA approval of supplemental filings related to product packaging and labeling and, in certain circumstances, the approval of Allergan. Nevertheless, we are currently undertaking significant preparations for expansion of our manufacturing and marketing capabilities in the event such approvals are obtained. If approved by the FDA, Vitrase® and Istalol™ will be manufactured for us through our contract manufacturers. In the United States the marketing of Istalol™ will be done by us and marketing for Vitrase®, for uses in the posterior region of the eye, will be done by Allergan, Inc.

We currently have no approved products. We are seeking FDA approval for Vitrase®, a proprietary drug that we are developing for the treatment of vitreous hemorrhage, for use as a spreading agent to facilitate the absorption and dispersion of other injected drugs, and for the treatment of diabetic retinopathy. We are also pursuing market approval in the United States of Istalol™, our new formulation of timolol, to treat glaucoma. In December 2003, we completed enrollment of our Phase III clinical studies in the United States for Xibrom™ (bromfenac), a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation and announced the initial results of our clinical studies in March 2004. Finally, we are currently conducting feasibility studies for the reformulation and commercialization of Caprogel® (aminocaproic acid), a topical formulation aminocaproic acid for the treatment of hyphema. We believe that if Vitrase®, Istalol™, and our other

ophthalmic product candidates obtain regulatory approval and are commercially successful, we will advance our strategic plan to build a specialty pharmaceutical company focused on serious diseases and conditions of the eye.

We currently have no products available for sale and have not generated any revenues from sales of our products. We have incurred losses since inception and had an accumulated deficit of $147.6 million through December 31, 2003. Our losses have resulted primarily from research and development activities, including clinical trials, related general and administrative expenses and a deemed dividend to our preferred shareholders. We expect to continue to incur operating losses for the foreseeable future as we continue to conduct research, development and clinical testing activities, and to seek regulatory approval for our product candidates and to develop our marketing, sales, distribution and other commercial and management capacities in anticipation of the approval of one or more of our product candidates.

Results of Operations

The following discussion of our results of operations generally reflects our continuing transition from a development-stage company to a specialty pharmaceuticals company with a primary focus on ophthalmology.

Years Ended December 31, 2003, 2002 and 2001

Revenue. Revenue of $278,000 for 2003 and 2002 reflects the amortization for the period of deferred revenue recorded in December 2001 for the license fee payment made by Otsuka Pharmaceuticals for commercialization rights to Vitrase® in Japan for ophthalmic uses in the posterior regions of the eye.

Research and development expenses. Research and development expenses were $17.3 million in 2003, $14.8 million in 2002 and $15.8 million in 2001. Our research and development expenses to date have consisted primarily of costs associated with the clinical trials of our product candidates, compensation and other expenses for research and development personnel, costs for consultants and contract research organizations and costs related to the development of commercial scale manufacturing capabilities for Vitrase®, Istalol™ and Xibrom™.

We generally classify and separate research and development expenditures into amounts related to preclinical research, clinical development and manufacturing development. We have not tracked our historical research and development costs by specific project. Instead, we track costs by the type of cost incurred.

In 2003, approximately 22% of our research and development expenditures were for preclinical research, approximately 52% was spent on clinical development and approximately 26% was spent on manufacturing development. Changes in our research and development expenses are primarily due to the following:

- Clinical Development Costs — Overall clinical costs for 2003 increased by $2.4 million from 2002. The increase in clinical costs in 2003 was due to the commencement of the Xibrom™ Phase III clinical trial. As a result, our overall clinical costs, which include clinical investigator fees, study monitoring costs and data management, increased in 2003 as compared to 2002.

- Regulatory Costs — Regulatory costs for 2003 increased by $300,000 from 2002. The increase is primarily attributable to the NDA filing fee associated with Vitrase® for use as a spreading agent.

- Direct Research Costs — Research costs for 2003 decreased by $2.4 million from 2002. This decrease is principally attributable to an overall reduction in development costs as our products advance further in the pipeline. Additionally, 2002 included the acquisition of three late-stage development compounds. The costs associated with such acquisition ($1.7 million) were immediately expensed as in-process research and development costs because there were no alternative future uses and did not otherwise quality for capitalization.

- Manufacturing Development Costs — Contract manufacturing costs for 2003 increased by $2.2 million from 2002. The increase in manufacturing development costs was due to increased development and/or manufacturing spending related to Vitrase®, Istalol™, and Xibrom™.

We anticipate that our research and development expenses for 2004 will be approximately the same as our research and development expenses for 2003, and will be focused primarily on further research and development of our product candidates. Our primary product candidates are Vitrase®, Istalol™, Xibrom™ and Caprogel®.

Vitrase® for the treatment of vitreous hemorrhage – On April 3, 2003, the FDA issued an approvable letter in which the FDA cited issues primarily related to the sufficiency of the efficacy data submitted with the NDA for Vitrase®. The FDA requested additional analysis of the existing data and an additional confirmatory clinical study based on that analysis. We have submitted information to the FDA in response to its non-clinical comments contained in the approvable letter and are

continuing to assess and discuss with the agency the clinical issues raised in the approvable letter. Based upon these discussions, we will determine the next appropriate steps in the approval process of Vitrase® for the treatment of vitreous hemorrhage.

Vitrase® for use as a spreading agent to facilitate the diffusion and absorption of injected drugs – In August 2003, we submitted to the FDA a second NDA for Vitrase® for use as a spreading agent to facilitate the dispersion and absorption of other drugs. The FDA granted "priority review" status for this NDA in August 2003 and accepted the NDA for filing and review in October 2003. In February 2004, the FDA notified us that it was extending the PDUFA action date 90 days to May 5, 2004. Based upon current discussions with the FDA, we believe that any remaining issues, and the FDA review, can be addressed within the revised time frame. The product we submitted in the second NDA is the same formulation as the product we submitted in the original NDA for the treatment of vitreous hemorrhage. The dose as a spreading agent is different than the dose used for injection into the posterior region of the eye. With respect to the second Vitrase® NDA, we are pursuing the development of additional package configurations for different dosages of the product to facilitate product utilization, improve profit margins and aid in obtaining appropriate third-party reimbursement. Upon approval of the second Vitrase® NDA, we intend to submit supplemental filings with the FDA with respect to such additional package configurations.

Vitrase® for the treatment of diabetic retinopathy – We have completed a patient pilot Phase II clinical study in Mexico City to evaluate the safety and efficacy of Vitrase® for the treatment diabetic retinopathy. The continued development of Vitrase® for the treatment of diabetic retinopathy is dependent upon a number of factors including among others, the FDA's evaluation of the Vitrase® NDAs for the treatment of vitreous hemorrhage and for use as a spreading agent, the successful completion of any additional clinical trials for the diabetic retinopathy indication and the continuing assessment of the market opportunity for this indication as compared to other product opportunities we may be pursuing at the time.

Istalol™ – Senju submitted a NDA for Istalol™ to the FDA in September 2002, which was accepted for review in November 2002. The NDA is based on data from a Phase I clinical study and a multi-center Phase III clinical trial conducted in the United States, as well as results from preclinical studies and Phase I and Phase II studies conducted in Japan. In July 2003, the FDA issued an approvable letter with respect to the Istalol™ NDA citing issues related to manufacturing methods and controls. No additional clinical studies were requested. We believe the issues cited by the FDA are addressable, and we are currently seeking qualification of an additional manufacturing site. In December 2003, we submitted to the FDA information seeking to qualify Bausch & Lomb Incorporated as an alternate manufacturer for Istalol. We expect a response from the FDA in the first half of 2004.

Xibrom™ – Phase I, Phase II and Phase III clinical studies have been completed in Japan and the product has been approved and was launched in 2000 in Japan. We completed our Phase III studies of Xibrom™ and announced initial results of our clinical studies in March 2004. Based on the initial results of our Phase III studies, we anticipate submitting a NDA for Xibrom™ in the second quarter of 2004.

Caprogel® – We are currently conducting feasibility studies for the reformulation and commercialization of Caprogel®. Once completed, and if these studies yield promising results, we intend to pursue further clinical development of Caprogel® consistent with such studies' results. However, the timing and scope for our development of Caprogel® may change based on our assessment, from time to time, of this product candidate's market potential, other product opportunities and our corporate priorities.

Our research and development activities reflect our efforts to advance our product candidates through the various stages of pre-clinical, clinical and regulatory product development. The expenditures that will be necessary to execute our development plans are subject to numerous uncertainties, which may affect our research and development expenditures and capital resources. For instance, the duration and the cost of clinical trials may vary significantly depending on a variety of factors including a trial's protocol, the number of patients in the trial, the duration of patient follow-up, the number of clinical sites in the trial, and the length of time required to enroll suitable patient subjects. Even if earlier results are positive, we may obtain different results in later stages of development, including failure to show the desired safety or efficacy, which could impact our development expenditures for a particular product candidate. Although we spend a considerable amount of time planning our development activities, we may be required to alter from our plan based on new circumstances or events or our assessment from time to time of a product candidate's market potential, other product opportunities and our corporate priorities. Any deviation from our plan may require us to incur additional expenditures or accelerate or delay the timing of our development spending. Furthermore, as we obtain results from trials and review the path toward regulatory approval, we may elect to discontinue development of certain product candidates in certain indications, in order to focus our resources on more promising candidates or indications.

Selling, general and administrative expenses. Selling, general and administrative expenses were $8.6 million in 2003, $8.2 million in 2002 and $7.5 million in 2001. The $400,000 increase in selling, general and administrative expenses in 2003

was a result of approximately $438,000 in directors' and officers' liability insurance premiums, $480,000 consultant related costs associated with increased activity with our product pipeline, $631,000 in marketing activities, offset by a $1.2 million decrease in deferred compensation related to stock-based compensation. The increase in general and administrative expenses in 2002 was primarily attributable to approximately $315,000 in directors and officers liability insurance premiums, $220,000 in the level of consultant related costs associated with our product acquisitions, with the remainder attributable to personnel expenses related to new management.

Stock-based compensation. Deferred compensation for stock options granted to employees and directors is the difference between the exercise price and the estimated fair value of the underlying common stock for financial reporting purposes on the date the options were granted. Deferred compensation is included as a component of stockholders' equity and is being amortized in accordance with Financial Accounting Standards Board Interpretation No. 28 (FIN 28), "Accounting for Stock Appreciation Rights and Other Variable Stock Option or Award Plans", over the vesting period of the related options, which is generally four years.

Compensation for stock options granted to non-employees has been determined in accordance with SFAS No. 123, "Accounting for Stock-Based Compensation", and Emerging Issues Task Force ("EITF") Consensus No. 96-18, "Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring or in Conjunction with Selling Goods or Services", as the fair value of the equity instrument issued and is periodically re-measured as the underlying options vest. Stock option compensation for non-employees is recorded as the related services are rendered and the value of compensation is periodically re-measured as the underlying options vest.

For the year ended December 31, 2003, we granted stock options to employees to purchase 536,150 shares of common stock at a weighted average exercise price of $5.84 per share, equal to the fair market value of our common stock at the time of grant. However, in previous years, we had granted stock options to employees with a grant price less than the fair market value at the date of grant. Therefore, we anticipate recording deferred compensation expense of approximately $423,000, $124,000 and $11,000 for the years ended December 31, 2004, 2005 and 2006 respectively, related to these option grants.

In connection with the grant of stock options to employees and directors, we recorded deferred compensation of approximately $110,000, $93,000 and $2,960,000 during the years ended December 31, 2003, 2002 and 2001, respectively, and recorded amortization of $956,000, $2,160,000 and $1,902,000 during the years ended December 31, 2003, 2002 and 2001, respectively.

Interest income. Interest income was $372,000 in 2003, $213,000 in 2002 and $826,000 in 2001. The increase in interest income in 2003 is primarily attributable to higher average cash balances on hand as compared to 2002. The decrease in interest income in 2002 over the prior year was primarily attributable to lower average cash balances on hand. We anticipate interest income to be lower in 2004 as compared to 2003 due to lower average cash balances in our short-term investment portfolio.

Interest expense. Interest expense was approximately $10,000 in 2003, $473,000 in 2002 and $25,000 in 2001. Interest expense incurred during 2003 was primarily attributable to the interest paid on the financing of our directors' and officers' insurance premiums. Interest expense incurred during 2002 was primarily attributable to approximately $412,000 related to the amortization of the fair value of the warrants issued in connection with the bridge loan in September 2002. Interest expense incurred during 2001 was primarily attributable to the interest paid on the financing of our directors' and officers' insurance premiums. We had no capital leases during 2001.

Income taxes. We incurred net operating losses in 2003, 2002 and 2001 and consequently did not pay any federal, state or foreign income taxes. At December 31, 2003, we had federal and California net operating loss carryforwards of approximately $95.5 million and $84.4 million, respectively, which we have fully reserved due to the uncertainty of realization. Our federal tax loss carryforwards will begin to expire in 2008, unless previously utilized. Our California tax loss carryforwards will begin to expire in 2004, unless previously utilized. We also have federal and California research tax credit carryforwards of approximately $4.6 million and $2.6 million, respectively. The federal research tax credits will begin to expire in 2010, unless previously utilized. Our California research tax credit carryforwards do not expire and will carryforward indefinitely until utilized. In addition, we have California manufacturers investment credit of approximately $30,000 that will begin to expire in 2010, unless previously utilized.

During 2002, a change in ownership, as described in the Internal Revenue Code Section 382, did occur and will limit our ability to utilize the net operating losses and tax credit carryforwards in the future.

Quarterly Results of Operations

The following table sets forth a summary of our unaudited quarterly operating results for each of the last eight quarters in the period ended December 31, 2003. This data has been derived from our unaudited consolidated interim financial statements which, in our opinion, have been prepared on substantially the same basis as the audited financial statements contained elsewhere in this report and include all normal recurring adjustments necessary for a fair presentation of the financial information for the periods presented. These unaudited quarterly results should be read in conjunction with our financial statements and notes thereto included elsewhere in this report. The operating results in any quarter are not necessarily indicative of the results that may be expected for any future period (in thousands except earnings per share).

	Quarter Ended							
	Dec. 31, 2003	Sept. 30, 2003	June 30, 2003	Mar. 31, 2003	Dec. 31, 2002	Sept. 30, 2002	June 30, 2002	Mar. 31, 2002
	(Unaudited)							
Revenue	$ 70	$ 69	$ 70	$ 69	$ 70	$ 68	$ 70	$ 70
Costs and expenses:								
Research and development	5,497	4,403	3,924	3,426	3,487	3,872	4,470	2,922
Selling, general and administrative	2,489	1,794	2,288	2,064	2,321	1,736	2,249	1,918
Total costs and expenses	7,986	6,197	6,212	5,490	5,808	5,608	6,719	4,840
Loss from operations	(7,916)	(6,128)	(6,142)	(5,421)	(5,738)	(5,540)	(6,649)	(4,770)
Interest income (expense), net	93	66	93	110	(349)	(41)	43	87
Net loss (1)	$ (7,823)	$ (6,062)	$ (6,049)	$ (5,311)	$ (6,087)	$ (5,581)	$ (6,606)	$ (4,683)
Net loss per common share, basic and diluted (1)	$ (0.51)	$ (0.46)	$ (0.45)	$ (0.40)	$ (0.86)	$ (3.30)	$ (3.93)	$ (2.82)

(1) As discussed in the Notes to the Consolidated Financial Statements, in November 2002 we completed a 1-for-10 reverse stock split to the then outstanding common stock. All historical common shares and per share data have been adjusted for the reverse stock split. Additionally, in November 2002 we consummated a private investment in public equity transaction, which resulted in the issuance of 10,526,306 shares of common stock and in November 2003, we completed a follow-on public offering, which resulted in the issuance of 4,000,000 shares of common stock.

Research & development expenses. During 2003, our quarterly research and development expenses increased primarily as a result of the commencement of the Xibrom™ Phase III clinical trial and increased development and/or manufacturing spending related to Vitrase®, Istalol™, and Xibrom™. During 2002, our quarterly research and development expenses decreased primarily as a result of the completion of our Phase III clinical trials for Vitrase® for the treatment of vitreous hemorrhage and the deferral of other development activities relating to our other product candidates. The decrease in activity during 2002 was offset by the acquisition costs related to the three late-stage development compounds from AcSentient during May 2002. The acquisition costs were expensed immediately as in-process research and development costs. Vitrase® development activities included the collection and review of clinical data from study sites around the world, improvements in the manufacturing process of our contract manufacturers and preparations for the submission of a NDA to the FDA.

Selling, general & administrative expenses. During 2003, our quarterly selling, general and administrative expenses increased primarily as a result of additional personnel expenses with the hiring of two additional key management employees and two additional executive employees, and other related facilities expenses. During 2002, our selling, general and administrative expenses increased primarily as a result of increases in personnel and operating expenses consisting of non-cash compensation associated with stock option grants, legal and accounting expenses relating to due diligence efforts for a potential acquisition, and personnel costs associated with the hiring of two additional executive employees.

Interest income (expense), net. During 2003, our quarterly net interest income increased from 2002 due to higher cash balances as a result of the PIPE transaction in November 2002 and the follow-on public offering in November 2003. During the fourth quarter of 2002, our interest expense increased significantly as a result of the amortization of the fair value attributable to the warrants issued in connection with the $4.0 million bridge loan in September 2002.

Net loss per common share, basic and diluted. Basic and diluted net loss per share computation for each quarter are independent and may not add up to the net loss per share computation for the respective year. See Note 1 of Notes to the Consolidated Financial Statements for an explanation of the determination of basic and diluted net loss per share.

Critical Accounting Policies and Estimates

Management's discussion and analysis of financial condition and results of operations, as well as disclosures included elsewhere in this Report are based upon our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. Actual results could differ from these estimates and could affect the reported amounts of assets, liabilities, revenues, expenses and related disclosure of contingencies.

We believe that the critical accounting policies that most impact the consolidated financial statements are as described below. A summary of our significant accounting policies is included in Note 1 to our consolidated financial statements which begin on page F-1.

We recognize revenue consistent with the provisions of the Securities and Exchange Commission's Staff Accounting Bulletin No. 101 (SAB 101), "Revenue Recognition", which sets forth guidelines in the timing of revenue recognition based upon factors such as passage of title, installation, payments and customer acceptance. Amounts received for product and technology license fees under multiple-element arrangements are deferred and recognized over the period of such services or performance if such arrangements require on-going services or performance. Amounts received for milestones are recognized upon achievement of the milestone, unless the amounts received are creditable against royalties or we have ongoing performance obligations. Royalty revenue will be recognized upon sale of the related products, provided the royalty amounts are fixed and determinable and collection of the related receivable is probable. Any amounts received prior to satisfying our revenue recognition criteria will be recorded as deferred revenue in the accompanying balance sheets.

We record a valuation allowance to reduce our deferred tax assets to the amount that is more likely than not to be realized. While we have considered future taxable income and ongoing prudent and feasible tax planning strategies in assessing the need for the valuation allowance, in the event we were to determine that we would be able to realize our deferred tax assets in the future in excess of its net recorded amount, an adjustment to the deferred tax asset would increase income in the period such determination was made.

Liquidity and Capital Resources

As of December 31, 2003, we had approximately $48.5 million in cash, cash equivalents and short-term investments and working capital of $44.2 million.

We have financed our operations since inception primarily through private equity sales and the sale of our common stock in our initial and follow-on public offerings. We received net proceeds of $10.0 million from the private sale of preferred stock in March 2000, $31.7 million from our initial public offering in August 2000, $4.0 million from the private sale of common stock in December 2001, $5.0 million from a license fee payment in December 2001, $4.0 million from the issuance of promissory notes in September 2002, $37.3 million from our PIPE transaction in November 2002 and $35.7 million from our follow-on public offering in November 2003. The PIPE transaction in November 2002 involved a private placement of 10,526,306 shares of our common stock for the aggregate purchase price of approximately $40.0 million, or $3.80 per share, and warrants to purchase up to 1,578,946 shares of our common stock for an exercise price of $3.80 per share. The follow-on public offering in November 2003 involved the sale of 4,000,000 shares of our common stock for the aggregate purchase price of $38.0 million, or $9.50 per share.

During 2003, we used $22.6 million of cash for operations principally as a result of the net loss of $25.2 million partially offset by non-cash compensation expense of $956,000. During 2002, we used $20.9 million of cash for operations principally as a result of the net loss of $23.0 million partially offset by non-cash compensation expense of $2.2 million. During 2001, we used $13.9 million of cash for operations principally as a result of the net loss of $22.5 million partially offset by the non-cash compensation expense of $1.9 million and $5.0 million in deferred income.

Net cash invested totaled $28.1 million during 2003 compared to $648,000 net cash invested during 2002. During 2001, $13.4 million of cash was provided by investing activities. Cash used for investing activities in 2003 is primarily attributable to the follow-on public offering of 4,000,000 shares of common stock at an aggregate purchase price of $38.0 million, or $9.50 per share. During 2002, the net cash invested was primarily attributable to the purchase of short-term investments.

Net cash provided by financing activities totaled $35.5 million during 2003 compared to $41.5 million in 2002 and $4.1 million in 2001. The net cash provided by financing activities in 2003 is primarily attributable to $35.7 million net proceeds from the public sale of 4,000,000 shares of common stock in November 2003, while the cash provided by financing activities in 2002 is primarily attributable to $4.0 million net proceeds from the issuance of a bridge loan in September 2002 and the $37.3 million net proceeds from the private sale of common stock to certain investors during November 2002.

We may be required to raise additional capital in the future through collaborative agreements, PIPE related financings, and various other public or private equity or debt financings. If we are required to raise additional capital in the future, there can be no assurance that the additional financing will be available on favorable terms, or at all.

We continually evaluate new opportunities for late-stage or currently marketed complementary product candidates and, if and when appropriate, intend to pursue such opportunities through the acquisitions of companies, products, or technology and our own research and development activities. Our ability to execute on such opportunities in some circumstances will be dependent, in part, upon our ability to raise additional capital on commercially reasonable terms. There can be no assurance that funds from these sources will be available when needed or, if available, will be on terms favorable to us or to our stockholders. If additional funds are raised by issuing equity securities, the percentage ownership of our stockholders will be

reduced, stockholders may experience additional dilution or such equity securities may provide for rights, preferences or privileges senior to those of the holders of our common stock.

Our actual future capital requirements will depend on many factors, including the following:

- receiving payments from Allergan and Otsuka with respect to our collaboration for the commercialization of Vitrase® for uses in the posterior region of the eye, including milestone payments, profit sharing and royalties;
- the rate of progress of our research and development programs;
- the results of our clinical trials and requirements to conduct additional clinical trials;
- the time and expense necessary to obtain regulatory approvals;
- activities and payments in connection with obtaining licenses for or acquisition of products;
- our ability to establish and maintain collaborative relationships;
- sales and marketing activities related to our product candidates;
- competitive, technological, market and other developments; and
- the success of the commercialization of our products.

Tabular Disclosure of Contractual Obligations

The following table summarizes our contractual obligations as of December 31, 2003:

		Payments due by period			
Contractual Obligations	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**More than 5 years**
Operating Lease Obligations	$639,000	$351,000	$194,000	$94,000	$ —
Total:	$639,000	$351,000	$194,000	$94,000	$ —

Visionex

Visionex was established in 1997, under the laws of Singapore, to engage in clinical, regulatory and marketing activities. During 1997, Visionex obtained from us the exclusive rights to register, import, market, sell and distribute Vitrase® and a product called Keraform® in East Asian markets, excluding Japan and Korea, for which Visionex paid us $5.0 million. Prior to our acquisition of Visionex (discussed below), investors who owned 66% of ISTA shares controlled 100% of Visionex shares.

On March 8, 2000, we acquired Visionex by entering into an agreement with Visionex shareholders whereby we issued 3,319,363 shares of our Series C preferred stock, convertible into 245,879 shares of our common stock, to acquire all of the outstanding capital stock of Visionex. We assigned a fair value of $11.70 per share to the 3,319,363 shares of Series C preferred stock issued to effect the acquisition, at which time we recorded a deemed dividend of $19.2 million to recognize the excess of the value of the shares issued over the net assets acquired.

Under Singapore tax law, Visionex was subject to a 15% withholding tax on a $5.0 million license that it paid to us in connection with a license to market, sell and distribute our Vitrase® and corneaplasty products in certain countries in Southeast Asia. This withholding tax was waived by the Economic Development Board, or EDB, of Singapore subject to various conditions, including a commitment that Visionex would implement a proposed project to expand its business activities in Singapore to the benefit of the local economy. We substantially wound down Visionex operations in July 2002, and the proposed project was never implemented. Based upon a letter we received from the EDB and our assessment of our obligations with the EDB, management does not believe that we will be required to pay any withholding tax or related obligations in connection with the license fee. However, if we are required to pay this withholding tax, our financial condition will suffer.

New Accounting Pronouncement

In December 2002, the FASB issued SFAS No. 148, "Accounting for Stock-Based Compensation – Transition and Disclosure." SFAS No. 148 is an amendment to SFAS No. 123 providing alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation and also provides additional disclosures about the method of accounting for stock-based employee compensation. Amendments are effective for our

financial statements beginning January 1, 2003. We have currently chosen to not adopt the voluntary change to the fair value based method of accounting for stock-based employee compensation. If we should choose to adopt such a method, its implementation pursuant to SFAS No. 148 could have a material effect on our consolidated financial position and results of operations.

Item 7A: Quantitative and Qualitative Disclosures about Market Risk

The primary objective of our investment activities is to preserve principal while at the same time maximizing the income we receive from our investments without significantly increasing risk. Some of the securities that we invest in may have market risk. This means that a change in prevailing interest rates may cause the principal amount of the investment to fluctuate. For example, if we hold a security that was issued with a fixed interest rate at the then-prevailing rate and the prevailing interest rate later rises, the principal amount of our investment will probably decline. To minimize this risk in the future, we intend to maintain our portfolio of cash equivalents and short-term investments in a variety of securities, including commercial paper, money market funds, government and non-government debt securities. The average duration of all of our investments in 2003 was less than one year. Due to the short-term nature of these investments, we believe we have no material exposure to interest rate risk arising from our investments. A hypothetical 100 basis point adverse move in interest rates along the entire interest rate yield curve would not materially affect the fair market value of our interest sensitive financial investments. Declines in interest rates over time will, however, reduce our investment income, while increases in interest rates over time will increase our interest expense. Historically, and as of December 31, 2003, we have not used derivative instruments or engaged in hedging activities.

We have operated primarily in the United States and have had no sales to date. Accordingly, we have not had any significant exposure to foreign currency rate fluctuations. Visionex's functional currency is the Singapore dollar and a portion of Visionex's business was conducted in currencies other than the Singapore dollar prior to the wind down of operations in July 2002. As a result, currency fluctuations between the Singapore dollar and the currencies in which Visionex had done business will cause foreign currency translation gains and losses. We do not expect our foreign currency translation gains or losses to be material. We do not currently engage in foreign exchange hedging transactions to manage our foreign currency exposure.

Item 8: Financial Statements and Supplemental Data

The consolidated financial statements and supplementary data required by this item are set forth on the pages indicated in Item 15 (a).

Item 9: Changes and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A: Disclosure Controls and Procedures

An evaluation as of the end of the period covered by this report was carried out, under the supervision and participation of management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures. Based upon that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures are effective in timely alerting them to material information required to be included in our periodic SEC filings.

PART III

Item 10: Directors and Executive Officers of the Registrant

Directors

Pursuant to our Amended and Restated Certificate of Incorporation and Bylaws, our Board of Directors currently consists of nine persons, divided into three classes serving staggered terms of three years. The Class I directors, Peter Barton Hutt, Benjamin F. McGraw III, Pharm.D. and Liza Page Nelson, are scheduled to serve until the annual meeting of stockholders in 2004. The Class II directors, Vicente Anido, Jr., Ph.D., Kathleen D. LaPorte, and Richard C. Williams, are scheduled to serve until the annual meeting of stockholders in 2005. The Class III directors, Jeffrey L. Edwards, Robert G. McNeil, Ph.D., and Wayne I. Roe, are scheduled to serve until the annual meeting of stockholders in 2006.

The following table sets forth the names, ages, principal occupations and year of appointment of our directors:

Name	Age	Principal Occupation	Director Since
Class I Directors			
Peter Barton Hutt	69	Partner, Covington & Burling	2002
Benjamin F. McGraw III, Pharm.D.	55	President and Chief Executive Officer, Valentis, Inc.	2000*
Liza Page Nelson	44	Managing Director, Investor Growth Capital	2002
Class II Directors			
Vicente Anido, Jr., Ph.D.	51	President and Chief Executive Officer	2001
Kathleen D. LaPorte	42	General Partner, Sprout Group	2002
Richard C. Williams	60	President, Conor-Thoele Limited	2002
Class III Directors			
Jeffrey L. Edwards	43	Corporate Vice President, Corporate Development, Allergan, Inc.	2002
Robert G. McNeil, Ph.D.	61	General Partner, Sanderling Ventures	1993
Wayne I. Roe	54	Retired	1998*

* Mr. McGraw and Mr. Roe resigned as directors of ISTA on November 19, 2002 with the closing of its PIPE transaction and were reappointed as directors in December 2002.

Vicente Anido, Jr., Ph.D. has served as our President and Chief Executive Officer and on our Board of Directors since December 2001. From June 2000 to September 2001, Dr. Anido was general partner for Windamere Venture Partners. From 1996 to 1999, Dr. Anido served as President and Chief Executive Officer of CombiChem, Inc., a biotechnology company. From 1993 to 1996, he served as President of the Americas Region of Allergan, Inc., a specialty pharmaceutical company focusing on ophthalmology, dermatology and neuromuscular indications. Dr. Anido is also a director of Apria Healthcare, Inc. Dr. Anido received a Ph.D. in Pharmacy Administration from the University of Missouri.

Peter Barton Hutt has served on our Board of Directors since November 2002. Mr. Hutt is a partner specializing in food and drug law in the Washington, D.C. law firm of Covington & Burling. Mr. Hutt joined Covington & Burling in 1960 and was named partner in 1968, leaving from 1971 to 1975 to serve as Chief Counsel for the Food and Drug Administration and returning to Covington & Burling in September 1975. Mr. Hutt is the co-author of the casebook used to teach Food and Drug Law throughout the country and teaches a full course on the subject annually at Harvard Law School. Mr. Hutt received a B.A. from Yale University and an LL.B. from Harvard University. In addition, Mr. Hutt received a Master of Laws degree in Food and Drug Law from New York University Law School.

Kathleen D. LaPorte has served on our Board of Directors since November 2002. Mrs. LaPorte is a General Partner in the Healthcare Technology Group of the Sprout Group located in Menlo Park, California. Mrs. LaPorte joined the Sprout Group in 1993 and became a General Partner in 1994. Between 1987 and 1993, Mrs. LaPorte was a principal at Asset Management Company, a venture capital firm focused on early-stage investments. Previously, Mrs. LaPorte was a financial

analyst with The First Boston Corporation. Mrs. LaPorte received a B.S. from Yale University and an M.B.A. from Stanford University Graduate School of Business. Sprout Capital has a contractual right to designate a representative to be nominated to our Board of Directors. Mrs. LaPorte is the designated representative of Sprout Group.

Benjamin F. McGraw, III, Pharm.D. has served on our Board of Directors since April 2000, except for the period from November 2002 to December 2002. Dr. McGraw has been President, Chief Executive Officer, and Chairman of the Board of Directors of Valentis, Inc., a biotechnology company, since 1994. Dr. McGraw received a Pharm.D. from the University of Tennessee.

Liza Page Nelson has served on our Board of Directors since November 2002. Ms. Nelson is a Managing Director and Co-Head of Healthcare investing activities for Investor Growth Capital, Inc. Prior to joining Investor Growth Capital in 1998, from 1988 to 1998, Ms. Nelson held a series of positions with increasing responsibility in corporate finance, strategic planning, contracting, marketing, business development and operating management at Pfizer, Inc. Prior to joining Pfizer, Ms. Nelson was with the Boston Consulting Group and E.M. Warburg, Pincus & Co. Ms. Nelson received a B.A. degree in Economics from Wesleyan University and an M.B.A. in Finance and Marketing from the Yale School of Management. Investor Growth Capital Limited has a contractual right to designate a representative to be nominated to our Board of Directors. Ms. Nelson is the designated representative of Investor Growth Capital Limited.

Richard C. Williams has served on our Board of Directors since November 2002. Since 1989, Mr. Williams has served as the founder and President of Conor-Thoele Limited, a consulting and financial advisory firm specializing in the healthcare industry and pharmaceutical segment. From 2000 to April 2001, Mr. Williams also served as Vice Chairman-Strategic Planning and director of King Pharmaceuticals, Inc. From 1992 to 2000, Mr. Williams served as Chairman and director of Medco Research, a cardiovascular pharmaceutical development company, prior to its acquisition by King Pharmaceuticals in 2000. From 1997 to 1999, Mr. Williams was Co-Chairman and a director of Vysis, a genetic biopharmaceutical company. Prior to founding Conor-Thoele Limited, Mr. Williams held various operational and financial management officer positions with Erbamont, N.V., Field Enterprises, Inc., Abbott Laboratories and American Hospital Supply Corporation. Mr. Williams is Chairman and a director of Cellegy Pharmaceuticals, Inc. Mr. Williams is also a director of EP Med Systems. Mr. Williams received a B.A. degree from DePauw University and an M.B.A. from the Wharton School of Finance.

Jeffrey L. Edwards has served on our Board of Directors since November 2002. Mr. Edwards is currently Corporate Vice President, Corporate Development for Allergan and has served in other capacities, including Senior Vice President Treasury, Tax and Investors Relations since 1993. Prior to Allergan, Mr. Edwards was with Banque Paribas and Security Pacific National Bank, where he held various senior level positions in the credit and business development departments. Mr. Edwards received a B.A. in Sociology from Muhlenberg College. Allergan has a contractual right to designate a representative to be nominated to our Board of Directors. Mr. Edwards is the designated representative of Allergan. From time to time, at our request, Mr. Edwards is excused from all or portions of our Board meetings that deal with subject matters that would not be in our best interests to be known by our competitors, including Allergan.

Robert G. McNeil, Ph.D. has served on our Board of Directors since 1993 and as our Chairman of the Board since 1995. Dr. McNeil has been a general partner with Sanderling Venture Partners, an investment firm specializing in the development of biomedical companies, since 1979. Dr. McNeil received a Ph.D. in Molecular Biology, Biochemistry and Genetics from the University of California, Irvine. Sanderling Venture Partners has a contractual right to designate a representative to be nominated to our Board of Directors. Mr. McNeil is the designated representative of Sanderling Venture Partners.

Wayne I. Roe has served on our Board of Directors since June 1998, except for the period from November 19, 2002 to December 2002. Mr. Roe was Senior Vice President for United Therapeutics, Inc., a biotechnology company, from November 1999 to November 2000. From November 1988 to March 1999, Mr. Roe founded and served in various management positions at Covance Health Economics and Outcome Services, a consulting firm for life sciences companies, last serving as Chairman of the Board of Directors. Mr. Roe is also currently a director of Aradigm Corporation, a developer of drug delivery systems. Mr. Roe received an M.A. in Political Economy from the State University of New York and an M.A. in Economics from the University of Maryland.

Other Executive Officers

William S. Craig, Ph.D. (53) has served as our Vice President, Research and Product Development since March 2001. From 1996 to December 1999, Dr. Craig was Vice President, Research and Development for Alpha Therapeutics Corporation, a biotechnology company. From 1988 to 1996 he was Senior Director Research and Development for Telios Pharmaceuticals, Inc., a biotechnology company. Dr. Craig received a Ph.D. in Chemistry from the University of California, San Diego.

Marvin J. Garrett (53) has served as our Vice President, Regulatory Affairs, Quality & Compliance since February 1999. From May 1994 to February 1999, Mr. Garrett was Vice President, Regulatory Affairs and Clinical Research for Xoma, Ltd., a biotechnology company. From 1990 to 1994, he was President and General Manager of Coopervision Pharmaceutical; a division of the Cooper Companies, Inc. Mr. Garrett received a B.S. in Microbiology from California State University Long Beach.

Lisa R. Grillone, Ph.D. (54) has served as our Vice President, Clinical Research and Medical Affairs since August 2000. From 1990 to July 2000, Dr. Grillone served in various drug development positions with ISIS Pharmaceuticals, Inc., a biotechnology company, last serving as Executive Director, Intellectual Property Licensing. Dr. Grillone received a Ph.D. in Cell Biology and Anatomy from New York University.

Kirk McMullin (50) has served as Vice President, Operations since August 2002. From 1995 to 2002, Mr. McMullin was Vice President, Worldwide Manufacturing Support for Allergan. Mr. McMullin received a B.A. from Humboldt State University.

Thomas A. Mitro (46) has served as our Vice President, Sales & Marketing since July 2002. From 1980 to 2002, Mr. Mitro held several positions at Allergan, including Vice President, Skin Care, Vice President, Business Development and Vice President, e-Business. Mr. Mitro received a B.S. degree from Miami University.

Lauren P. Silvernail, (45) has served as our Chief Financial Officer and Vice President, Corporate Development, since March 2003. From 1995 to March 2003, Mrs. Silvernail served in various operating and corporate development positions for Allergan, most recently serving as Vice President, Business Development. From 1989 to 1994 she was a general partner at Glenwood Ventures and served as a director and operating manager for several portfolio companies. Mrs. Silvernail received an M.B.A. from the University of California, Los Angeles.

Kathleen McGinley, (54) has served as our Vice President, Human Resources and Corporate Facilities, since November 2003. From January 2003 to November 2003, Ms. McGinley served as a consultant to ISTA . From May 2000 to January 2003, Ms. McGinley served as Director and Vice President, Human Resources for Littlefeet, Inc. From 1999 to May 2000 she served as Director of Human Resources for Combi-Chem/Dupont Pharmaceuticals in San Diego, CA. Ms. McGinley received an M.S. from the University of Tennessee, Knoxville.

Family Relationships

There are no family relationships between any of our directors or executive officers.

Involvement in Certain Legal Proceedings

ISTA knows of no event which occurred during the past five years and which is described in Item 401(f) of Regulation S-K relating to any of our directors or officers.

Audit Committee and Audit Committee Financial Expert

The members of the Audit Committee of the Board of Directors (the "Audit Committee") are Richard C. Williams (Chairman), Benjamin F. McGraw, III, Pharm.D., and Wayne I. Roe, all of whom meet the definition of "independence" set forth in the NASDAQ corporate governance listing standards. The Board of Directors has also designated Mr. Williams and Dr. McGraw as our "audit committee financial experts," as defined by the rules of the SEC. The Audit Committee's responsibilities include: (i) reviewing the independence, qualifications, services, fees, and performance of the independent auditors, (ii) appointing, replacing and discharging the independent auditors, (iii) pre-approving the professional services provided by the independent auditors, (iv) reviewing the scope of the annual audit and reports and recommendations submitted by the independent auditors, and (v) reviewing ISTA's financial reporting and accounting policies, including any significant changes, with management and the independent auditors.

Code of Ethics and Conduct

We have adopted a Code of Ethics and Conduct that is applicable to all of our directors, officers and employees and have posted this Code of Ethics and Conduct on our website at www.istavision.com.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), requires our directors, officers and beneficial owners of more than 10% of our Common Stock to file reports of ownership and reports of changes in the ownership with the Securities and Exchange Commission. Such persons are required by Securities Exchange Commission regulations to furnish us with copies of all Section 16(a) forms they file.

Based solely on our review of the copies of such forms submitted to us during the year ended December 31, 2003 (the "Last Fiscal Year"), we believe that all Section 16(a) filing requirements applicable to our officers and directors were complied with, except that Robert G. McNeil filed late one Form 4, Kathleen D. LaPorte filed late one Form 4, Liza Page Nelson filed late one Form 4, Wayne I. Roe filed late one Form 4, Richard C. Williams filed late one Form 4, Benjamin F. McGraw III filed late one Form 4 and Peter Barton Hutt filed late one Form 4.

Item 11: Executive Compensation

Summary Compensation Table

The following table sets forth information for the years ended December 31, 2001, 2002 and 2003 regarding the compensation of our Chief Executive Officer and each of our four other most highly compensated executive officers whose total annual salary and bonus for such fiscal years were in excess of $100,000 (collectively, the "Named Executive Officers").

		Annual Compensation		Long-Term Compensation Awards Securities Underlying	All Other Compensation
Name and Principal Position	Year	Salary ($)	Bonus ($)	Options	($)
Vicente Anido, Jr., Ph.D	2001	15,417(1)	—	100,461	—
President and Chief Executive Officer	2002	370,000	—	595,000	2,717*
	2003	381,100	138,750	—	5,000*
Marvin J. Garrett	2001	230,450	24,750	3,500	6,219*
Vice President, Regulatory Affairs,	2002	240,820	25,926	140,000	5,000*
Quality and Compliance	2003	252,871	60,000	—	5,000*
Thomas A. Mitro	2002	117,500(2)	—	194,000	2,067*
Vice President, Sales and Marketing	2003	239,700	60,000	—	5,000*
William S. Craig, Ph.D.	2001	220,000	21,874	6,000	2,500*
Vice President, Research and	2002	228,800	16,500	66,500	1,990*
Product Development	2003	235,700	45,000	—	5,000*
Lisa R. Grillone, Ph.D.	2001	219,614	13,439	3,500	3,340*
Vice President, Clinical Research	2002	231,000	24,707	148,250	4,267*
and Medical Affairs	2003	245,000	58,000	—	5,000*

* Life insurance or medical benefits.

(1) Dr. Anido joined ISTA in December 2001. His annualized salary for 2001 was $370,000.

(2) Mr. Mitro joined ISTA in July 2002. His annualized salary for 2002 was $235,000.

Option Grants

Option Grants During Last Fiscal Year. There were no options granted during the fiscal year ended December 31, 2003 to any of the Named Executive Officers.

Option Exercises in Last Fiscal Year and Fiscal Year End Option Values. The following table sets forth the information with respect to stock option exercises during the year ended December 31, 2003, by the Named Executive Officers, and the number and value of securities underlying unexercised options held by the Named Executive Officers at December 31, 2003.

Aggregate Option Exercises in Fiscal 2003 and Year-End Option Values

Name	Shares Acquired Upon Exercise (#)	Value Realized ($)	Number of Securities Underlying Unexercised Options At December 31, 2003 (#)		Value of Unexercised In-the-Money Options at December 31, 2003 (1)	
			Exercisable	Unexercisable	Exercisable	Unexercisable
Vicente Anido, Jr., Ph.D.	—	—	198,980	496,481	$ 861,256	$ 2,583,793
Marvin J. Garrett	—	—	79,520	81,017	$ 378,794	$ 449,530
Thomas A. Mitro	—	—	52,249	141,751	$ 246,159	$ 726,801
William S. Craig, Ph.D.	—	—	37,619	41,177	$ 174,802	$ 212,377
		—	73,043	84,957	$ 354,638	$ 455,963

(1) Closing price of our Common Stock at fiscal year-end minus the exercise price. The fair market value of our Common Stock at the close of business on December 31, 2003, was $9.28.

Compensation of Directors

Our non-employee directors currently receive $2,500 in cash compensation from us for their service as members of the Board of Directors for each board meeting attended and $1,000 for each committee meeting attended; provided, however that directors only receive $500 for telephonic attendance at any board or committee

meeting. All non-employee directors are reimbursed for travel and miscellaneous expenses in connection with attendance at board and committee meetings. Liza Page Nelson and Jeffrey Edwards have each declined any cash compensation for their respective service as a member of ISTA's Board of Directors.

Our 2000 Stock Plan provides for initial option grants to purchase 32,500 shares of our Common Stock to each non-employee director upon their appointment to the board and subsequent annual grants after 2003 to purchase 16,250 shares of our Common Stock. During 2003, we granted our non-employee directors options to purchase 113,750 shares of Common Stock each at an exercise price of $6.96 per share. The shares subject to the initial option grants vest in three equal annual installments while the shares subject to the subsequent annual grants are fully vested when granted. Jeffrey Edwards has declined option grants for his service as a member of our Board of Directors.

Employment and Change in Control Agreements

We have entered into an employment agreement with Dr. Anido. Dr. Anido's employment agreement sets forth his compensation arrangements, including his initial annual base salary and initial option grant. Dr. Anido is also entitled to a performance bonus of up to 50% of his salary. In the event of termination of employment other than voluntarily or for cause, Dr. Anido will receive nine months of base salary as severance; provided that, in the event such termination occurs after a "change of control" of ISTA, Dr. Anido will receive twenty-four months of base salary as severance and all outstanding options to purchase our common stock then held by Dr. Anido will become fully vested and exercisable.

We have entered into change of control severance agreements with the following executive officers: Mr. Mitro, Mr. Garrett, Dr. Craig, Dr. Grillone, Mr. McMullin, Mrs. Silvernail and Ms. McGinley. Each of these agreements provides that if the executive's employment is terminated as a result of an "involuntary termination" within 24 months after a "change of control," the executive will be entitled to nine months of base salary and healthcare related benefits and a pro rata portion of his or her performance bonus based upon the number of months that such employee was employed during the year of termination. In addition, all options to purchase our Common Stock held by the executive at the time of such termination shall vest in full.

Compensation Committee Interlocks and Insider Participation

During 2003, no member of the Compensation Committee was an officer or employee of ISTA. During 2003, no member of the Compensation Committee or executive officer of ISTA served as a member of the Board of Directors or Compensation Committee of any entity that has an executive officer serving as a member of our Board of Directors or Compensation Committee.

Compensation Committee Report on Executive Compensation

Notwithstanding anything to the contrary in any of our previous or future filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, that might incorporate this Annual Report on Form 10-K or future filings with the Securities Exchange Commission, in whole or in part, the foregoing Committee Report shall not be "soliciting material" or "filed" with the Securities Exchange Commission, nor shall such information be incorporated by reference into any such filing.

The Compensation Committee of the Board of Directors (the "Committee"), comprising three non-employee directors, is responsible for the administration of our executive compensation programs. These programs include base salary for executive officers and both annual and long-term incentive compensation programs. Our compensation programs are designed to provide a competitive level of total compensation and include incentive and equity ownership opportunities linked to our performance and stockholder return.

Compensation Philosophy. Our overall executive compensation philosophy is based on a series of guiding principles derived from our values, business strategy, and management requirements. These principles are summarized as follows:

- Provide competitive levels of total compensation which will enable us to attract and retain the best possible executive talent;
- Motivate executives to achieve optimum performance for us;
- Align the financial interest of executives and stockholders through equity-based plans; and
- Provide a total compensation program that recognizes individual contributions as well as overall business results.

Compensation Program. The Committee is responsible for reviewing and recommending to the Board the compensation and benefits of all of our officers and the general policies relating to compensation and benefits of our employees. The Committee is also responsible for the administration of the 2000 Stock Plan. There are two major components to our executive compensation: base salary and potential cash bonus, as well as potential long-term compensation in the form of stock options. The Committee considers the total current and potential long-term compensation of each executive officer in establishing each element of compensation.

1. Base Salary. In setting compensation levels for executive officers, the Committee reviews competitive information relating to compensation levels for comparable positions at biotechnology, pharmaceutical and high technology companies. In addition, the Committee may, from time to time, hire compensation and benefit consultants to assist in developing and reviewing overall salary strategies. Individual executive officer base compensation may vary based on time in position, assessment of individual performance, salary relative to internal and external equity and critical nature of the position relative to our success.

2. Long-Term Incentives. Our 2000 Stock Plan provides for the issuance of stock options to our officers and employees to purchase shares of our Common Stock at an exercise price equal to the fair market value of such stock on the date of grant. Stock options are granted to our executive officers and other employees both as a reward for past individual and corporate performance and as an incentive for future performance. The Committee believes that stock-based performance compensation arrangements are essential in aligning the interests of management and the stockholders in enhancing the value of our equity.

2003 Compensation for the Chief Executive Officer. In determining Dr. Anido's salary for 2003, the Board of Directors considered competitive compensation data for chief executive officers and presidents of similar companies within the biotechnology and pharmaceutical industry, taking into account Dr. Anido's experience and knowledge. The Board of Directors determined that it was appropriate to offer an annual salary of $381,100 for 2003.

Section 162(m) of the Internal Revenue Code Limitations on Executive Compensation. Section 162(m) of the United States Internal Revenue Code of 1986, as amended, (the "Code") may limit our ability to deduct for United States federal income tax purposes compensation in excess of $1,000,000 paid to the our Chief Executive Officer and our four other highest paid executive officers in any one fiscal year. None of our executive officers received any such compensation in excess of this limit during fiscal 2003. Grants under the 2000 Stock Plan will not be subject to the deduction limitation, including the option grant limitations described below.

Section 162(m) of the Code places limits on the deductibility for United States federal income tax purposes of compensation paid to certain of our executive officers. In order to preserve our ability to deduct the compensation income

associated with options granted to such person, for the purposes of Section 162(m) of the Code, the 2000 Stock Plan provides that no employee may be granted, in any of our fiscal years, options to purchase more than 100,000 shares of Common Stock. In addition, the 2000 Stock Plan provides that in connection with an employee's initial employment, the employee may be granted an additional 200,000 shares of Common Stock. To the extent grants under the 2000 Stock Plan are in excess of these limitations, such excess shall not be exempt from the deductibility limits of Section 162(m) of the Code.

Respectfully submitted,

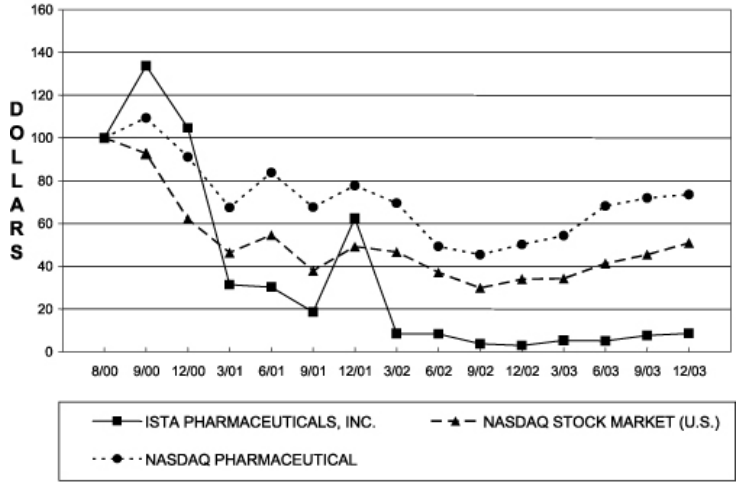
Benjamin F. McGraw III, Pharm.D.,
Chairman
Kathleen D. LaPorte
Liza Page Nelson

Stock Performance Graph

The following graph compares our total cumulative stockholder return as compared to the Nasdaq National Market and U.S. index ("Nasdaq U.S. Index") and the Nasdaq Pharmaceutical Index for the period beginning on August 22, 2000, our first day of trading after our initial public offering, and ending on December 31, 2003. Total stockholder return assumes $100.00 invested at the beginning of the period in our Common Stock, the stocks represented by the Nasdaq U.S. Index and the Nasdaq Pharmaceutical Index, respectively. Total return assumes reinvestment of dividends; we have paid no dividends on our Common Stock.

COMPARISON OF 40 MONTH CUMULATIVE TOTAL RETURN*

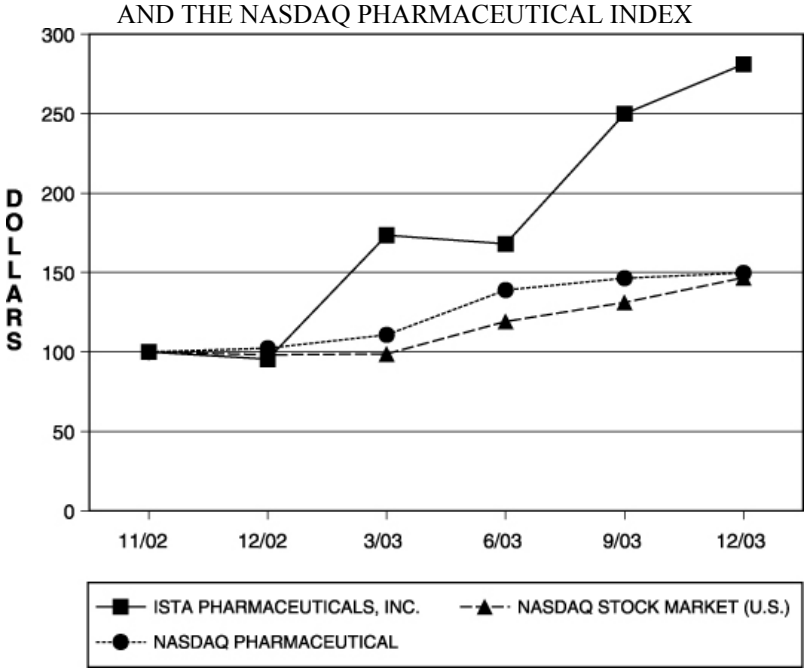
AMONG ISTA PHARMACEUTICALS, INC., THE NASDAQ STOCK MARKET (U.S.) INDEX
AND THE NASDAQ PHARMACEUTICAL INDEX



* $100 invested on 8/22/00 in stock or index-
including reinvestment of dividends.
Fiscal year ending December 31.

COMPARISON OF 13 MONTH CUMULATIVE TOTAL RETURN*

AMONG ISTA PHARMACEUTICALS, INC., THE NASDAQ STOCK MARKET (U.S.) INDEX
AND THE NASDAQ PHARMACEUTICAL INDEX



***$100 invested on 11/13/02 in stock or index-**
including reinvestment of dividends.
Fiscal year ending December 31.

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

The following table sets forth the beneficial ownership of our Common Stock as of March 17, 2004, by (i) each person or entity who is known by us to own beneficially more than 5% of the outstanding shares of Common Stock, (ii) each of our directors, (iii) each of the executive officers named in the Summary Compensation Table, and (iv) all of our directors and executive officers as a group.

Name of Beneficial Owner	Number of shares outstanding	Number of shares underlying options	Approximate Percent Owned (1)
DIRECTORS AND NAMED EXECUTIVE OFFICERS			
Peter Barton Hutt	—	10,834	*
Benjamin F. McGraw III, Pharm.D.	—	16,510	*
Liza Page Nelson (2)	3,952,630	10,834	22.0%
Vicente Anido, Jr., Ph.D	—	274,829	1.5%
Kathleen D. LaPorte (3)	5,163,155	10,834	28.5%
Richard C. Williams.	—	10,834	*
Jeffrey L. Edwards.	—	—	*
Robert G. McNeil, Ph.D (4)	1,654,247	14,778	9.5%
Wayne I. Roe.	—	19,442	*
Marvin J. Garrett	—	92,045	*
Thomas A. Mitro	—	73,393	*
William S. Craig, Ph.D.	—	44,568	*
Lisa R. Grillone, Ph.D.	—	87,227	*
All directors and executive officers as a group (16 persons)	10,770,032	685,385	64.3%
5% STOCKHOLDERS			
Investor Growth Capital Limited	2,766,841	—	15.8%
Investor Group LP	1,185,789	—	6.8%
Sprout Capital IX LP	4,897,342	—	28.1%

* Less than 1%

(1) Beneficial ownership is determined in accordance with the rules of the Securities and Exchange Commission. Applicable percentage ownership is based on 17,456,678 shares of Common Stock as of March 17, 2004. Shares of Common Stock subject to options and warrants currently exercisable, or exercisable within 60 days of March 17, 2004, are deemed outstanding for computing the percentage of any other person. Except as otherwise noted, the stockholders named in the table have sole voting and investment power with respect to all shares of Common Stock shown as beneficially owned by them, subject to applicable community property laws.

(2) Consists of 2,766,841 shares (including 372,105 shares issuable upon exercise of warrants) of Investor Growth Capital Limited and 1,185,789 shares (including 159,474 shares issuable upon exercise of warrants) of Investor Group L.P. Ms. Nelson is a Managing Director and Co-Head of Healthcare Investing Activities for Investor Growth Capital, Inc., an affiliate of Investor Growth Capital Limited and Investor Group, L.P. Ms. Nelson disclaims beneficial ownership except to the extent of her pecuniary interest therein. Ms. Nelson's business address is c/o Investor Growth Capital, 12 East 49th Street, 27th Floor, New York, New York 10017.

(3) Consists of 4,897,342 shares (including 653,978 shares issuable upon exercise of warrants) of Sprout Capital IX L.P., 19,298 shares (including 2,577 shares issuable upon exercise of warrants) of Sprout Entrepreneurs' Fund L.P. and 246,515 shares (including 32,919 shares issuable upon exercise of warrants) of Donaldson Lufkin & Jenrette Securities Corp. Ms. LaPorte is a General Partner in the Healthcare Technology Group of the Sprout Group, and is a Managing Director of DLJ Capital Corp., which is the Managing General Partner of Sprout Capital IX, L.P. and the General Partner of Sprout Entrepreneurs' Fund, L.P. Ms. LaPorte disclaims beneficial ownership except the extent of her pecuniary interest therein. Ms. LaPorte's business address is c/o The Sprout Group, 3000 Sand Hill Road, Suite 170, Menlo Park, California 94024.

(4) Consists of 302 shares owned by Sanderling IV Biomedical LP; 966 shares owned by Sanderling IV Biomedical Co. Investment Fund LP; 1,595 shares owned by Sanderling IV Limited Partnership; 118,900 shares (including 17,664 shares issuable upon exercise of warrants) owned by Sanderling V Beteiligungs GmbH & Co. KG; 495,973 shares (including 74,153 shares issuable upon exercise of warrants) owned by Sanderling V Biomedical Co-Investment Fund; 133,775 shares (including 20,001 shares issuable upon exercise of warrants) owned by Sanderling V Limited Partnership; 3,604 shares owned by Sanderling Venture Partners IV; 4,098 shares owned by Sanderling Venture Partners IV LP; 776 shares owned by Sanderling Venture; 818,081 shares (including 122,312 shares issuable upon exercise of warrants) owned by Sanderling Venture Partners V Co-Investment Fund; 6,098 shares owned by the John T. Parrish & Robert G. McNeil Joint Tenancy Trust; 511 shares owned by the Middleton McNeil Retirement Trust Robert G. McNeil; 65,461 shares (including 12,831 shares issuable upon exercise of warrants) owned by Robert G. McNeil c/o Sanderling Ventures; and 4,107 shares owned by the Middleton McNeil Retirement Trust F/B/O Robert G. McNeil. Dr. McNeil is a Managing Director of Middleton, McNeil & Mills Associates V., LLC, an affiliate of the Sanderling entities. Dr. McNeil disclaims beneficial ownership except the extent of his pecuniary interest therein. Dr. McNeil's business address is c/o Sanderling Venture Partners, 2730 Sand Hill Road, Suite 200, Menlo Park, California 94024.

Equity Compensation Plan Information

Plan category	(a) Number of securities to be issued upon exercise of outstanding options, warrants and rights	(b) Weighted-average exercise price of outstanding options, warrants and rights	(c) Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a)
Equity compensation plans approved by security holders (1)	2,163,155	$ 4.64	710,129
Equity compensation plans not approved by security holders	145,461	16.28	0
Total	2,308,616	$ 5.37	710,129

(1) Both our 2000 Stock Plan and our Employee Stock Purchase Plan provide for annual increases in the number of shares available for issuance under each plan on the first day of each year, beginning in 2003, equal to the lesser of 200,000 shares, 1.5% of the outstanding shares of common stock on the first day of the year, or a lesser amount as the Board of Directors may determine.

In December 2001, the Board of Directors granted our new Chief Executive Officer and President, as an inducement to his employment, a stand-alone option agreement to purchase 100,461 shares of our common stock for a purchase price of $20.00 per share. In June 2002, the Board of Directors granted our new Vice President, Sales & Marketing, as an inducement to his employment, a stand-alone option agreement to purchase 30,000 shares of common stock of the Company for a purchase price of $8.50. In August 2002, the Board of Directors granted our new Vice President, Operations, as an inducement to his employment, a stand-alone option agreement to purchase 15,000 shares of common stock of the Company for a purchase price of $6.90. Each option holder may purchase up to 25% of the shares under each option on the first anniversary of the option grant date and the right to purchase the remaining shares vests in equal monthly installments so that each option is fully vested four years after the date of grant.

Item 13: Certain Relationships and Related Transactions

There were no transactions in which the amount involved exceeded $60,000 and in which any director, executive officer or holder of more than 5% of our capital stock had or will have a direct or indirect material interest during the fiscal year ending December 31, 2003, other than compensation arrangements that are described under “Compensation of Directors” and “Executive Officer Compensation.”

Item 14: Principal Accountant Fees and Services

The following is a summary of the fees billed to ISTA by Ernst & Young LLP for professional services rendered for the fiscal years ended December 31, 2003 and December 31, 2002:

Fee Category	Fiscal 2003 Fees	Fiscal 2002 Fees
Audit Fees	$ 264,872	$ 197,297
Audit Related Fees	—	—
Tax Fees	13,191	40,580
All Other Fees	—	—
Total Fees	$ 278,063	$ 237,877

Audit Fees Consists of fees billed for professional services rendered for the audit of our consolidated financial statements ($102,409 in 2003, $89,788 in 2002) and review of the interim consolidated financial statements included in quarterly reports ($27,020 in 2003, $27,250 in 2002).

Audit-Related Fees Consists of fees billed for assurance and related services that are reasonably related to the performance of the audit or review of our consolidated financial statements and are not reported under “Audit Fees.” These services include consultations related to the Sarbanes-Oxley Act and consultations concerning financial accounting and reporting standards.

Tax Fees Consists of fees billed for professional services for tax compliance, tax advice and tax planning. These services include assistance related to state tax incentives.

All Other Fees Consists of all other non-audit services, including fees related to SEC filings.

The Audit Committee's policy is to pre-approve all audit and permissible non-audit services performed by the independent auditors. These services may include audit services, audit-related services, tax services and other services. For audit services, the independent auditor provides an engagement letter in advance of the February meeting of the Audit Committee, outlining the scope of the audit and related audit fees. If agreed to by the Audit Committee, this engagement letter is formally accepted by the Audit Committee at its February Audit Committee meeting.

For non-audit services, our senior management will submit from time to time to the Audit Committee for approval non-audit services that it recommends the Audit Committee engage the independent auditor to provide for the fiscal year. Our senior management and the independent auditor will each confirm to the Audit Committee that each non-audit service is permissible under all applicable legal requirements. A budget, estimating non-audit service spending for the fiscal year, will be provided to the Audit Committee along with the request. The Audit Committee must approve both permissible non-audit services and the budget for such services. The Audit Committee will be informed routinely as to the non-audit services actually provided by the independent auditor pursuant to this pre-approval process.

PART IV

Item 15: Exhibits, Financial Statement Schedules and Reports on Form 8-K

(a) Financial Statements

(1) Index to Consolidated Financial Statements

The financial statements required by this item are submitted in a separate section beginning on page F-1 of this report.

CONSOLIDATED FINANCIAL STATEMENTS OF ISTA PHARMACEUTICALS, INC.

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Consolidated Statements of Operations for the years ended December 31, 2003, 2002 and 2001 and the period from February 13, 1992 (inception) to December 31, 2003 ..... F-4
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(2) Financial Statement Schedules

None

(3) Exhibits

See Exhibit Index

(b) Reports on Form 8-K

1. On October 7, 2003, we filed a Form 8-K under Item 5, announcing that the U.S. Food and Drug Administration (FDA) accepted for filing and review its second New Drug Application (NDA) for Vitrase®. The NDA was submitted on August 5, 2003 seeking approval for use of Vitrase® as a spreading agent to facilitate the dispersion and absorption of other drugs.

2. On October 9, 2003, we filed a Form 8-K under Item 5, disclosing that we had filed a Registration Statement on Form S-2 (333-109576) with the Securities and Exchange Commission for the public offering of up to 4,000,000 shares of our common stock and 500,000 shares of common stock offered by selling stockholders. We also granted the underwriters an option to purchase an additional 675,000 shares to cover over-allotments.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form 10-K and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Irvine, State of California, on March 26, 2004.

By: /s/ VICENTE ANIDO, JR.
Vicente Anido, Jr., Ph.D.
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below constitutes and appoints each of Vicente Anido, Jr., Ph.D. and Lauren P. Silvernail as his or her attorney-in-fact, with full power of substitution, for him or her in any and all capacities, to sign any amendments to this Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each attorney-in-fact, or his substitute, may do or cause to be done by virtue hereof.

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

Signature	Title	Date
/s/ VICENTE ANIDO, JR. Vicente Anido, Jr., Ph.D.	President, Chief Executive Officer and Director	March 26, 2004
/s/ LAUREN P. SILVERNAIL Lauren P. Silvernail	Chief Financial Officer and Vice President, Corporate Development	March 26, 2004
/s/ ROBERT G. McNEIL Robert G. McNeil, Ph.D.	Chairman of the Board	March 26, 2004
 Jeffrey L. Edwards	Director	March 26, 2004
/s/ BENJAMIN F. McGRAW III Benjamin F. McGraw III	Director	March 26, 2004
/s/ PETER BARTON HUTT Peter Barton Hutt	Director	March 26, 2004
/s/ KATHLEEN D. LaPORTE Kathleen D. LaPorte	Director	March 26, 2004
/s/ LIZA PAGE NELSON Liza Page Nelson	Director	March 26, 2004
/s/ RICHARD C. WILLIAMS Richard C. Williams	Director	March 26, 2004
/s/ WAYNE I. ROE Wayne I. Roe	Director	March 26, 2004

ISTA PHARMACEUTICALS, INC.

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REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors and Stockholders ISTA Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of ISTA Pharmaceuticals, Inc. (a development stage company) as of December 31, 2003 and 2002, and the related consolidated statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2003, and for the period from February 13, 1992 (inception) to December 31, 2003. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

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

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of ISTA Pharmaceuticals, Inc. (a development stage company) at December 31, 2003 and 2002, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2003, and for the period from February 13, 1992 (inception) to December 31, 2003, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

San Diego, California
February 20, 2004

ISTA PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	December 31, 2003	December 31, 2002
ASSETS		
Current assets:		
Cash and cash equivalents	$ 16,988	$ 32,257
Short-term investments	31,475	3,455
Other current assets	1,035	509
Total current assets	49,498	36,221
Property and equipment, net	649	879
Deposits and other assets	35	35
Total assets	$ 50,182	$ 37,135
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,072	$ 910
Accrued compensation and related expenses	699	687
Accrued expenses — clinical trials	476	721
Other accrued expenses	2,058	857
Total current liabilities	5,305	3,175
Deferred rent	9	10
Deferred income	4,444	4,722
Commitments		
Stockholders' equity:		
Common stock, $0.001 par value; 100,000,000 shares authorized at December 31, 2003 and 2002; 17,375,439 and 13,288,120 shares issued and outstanding at December 31, 2003 and 2002, respectively	17	13
Additional paid-in capital	188,621	153,022
Deferred compensation	(547)	(1,390)
Accumulated other comprehensive income	(28)	(23)
Deficit accumulated during the development stage	(147,639)	(122,394)
Total stockholders' equity	40,424	29,228
Total liabilities and stockholders' equity	$ 50,182	$ 37,135

See accompanying notes.

ISTA PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except share and per share data)

	Years Ended December 31,			For the Period From February 13, 1992 (Inception) To December 31, 2003
	2003	2002	2001	
Revenue	$ 278	$ 278	$ —	$ 556
Costs and expenses:				
Research and development	17,250	14,751	15,770	90,713
Selling, general and administrative	8,635	8,224	7,538	40,388
Total costs and expenses	25,885	22,975	23,308	131,101
Loss from operations	(25,607)	(22,697)	(23,308)	(130,545)
Interest income	372	213	826	2,999
Interest expense	(10)	(473)	(25)	(803)
Net loss	(25,245)	(22,957)	(22,507)	(128,349)
Deemed dividend for preferred stockholders	—	—	—	(19,245)
Net loss attributable to common stockholders	$ (25,245)	$ (22,957)	$ (22,507)	$ (147,594)
Net loss per common share, basic and diluted	$ (1.83)	$ (7.53)	$ (14.43)	
Shares used in computing net loss per common share, basic and diluted	13,802,540	3,048,679	1,559,388	

See accompanying notes.

ISTA PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
PERIOD FROM FEBRUARY 13, 1992 (INCEPTION) TO DECEMBER 31, 2003
(in thousands, except share and per share data)

	Convertible Preferred Stock		Common Stock		Additional Paid-in	Preferred and Common Stock Subscribed		Subscriptions	Deferred	Accumulated Other	Deficit Accumulated During the	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Shares	Amount	Receivable	Compensation	Comprehensive Income	Development Stage	Equity (Deficit)
Issuance of Series A preferred stock at $1.00 per share cash	295,000	$ 295	—	$ —	$ —	—	$ —	$ —	$ —	$ —	$ —	$ 295
Issuance of common stock at $.32 to $.1.80 per share for cash	—	—	95,000	—	60	—	—	—	—	—	—	60
Issuance of common stock at $.376 per share for intellectual property	—	—	13,333	—	5	—	—	—	—	—	—	5
Net loss	—	—	—	—	—	—	—	—	—	—	(121)	(121)
Balance at December 31, 1992	295,000	295	108,333	—	65	—	—	—	—	—	(121)	239
Issuance of Series A preferred stock at $1.00 per share for cash	539,375	539	—	—	—	—	—	—	—	—	—	539
Net loss	—	—	—	—	—	—	—	—	—	—	(471)	(471)
Balance at December 31, 1993	834,375	834	108,333	—	65	—	—	—	—	—	(592)	307
Issuance of common stock at $2.10 per share for cash	—	—	13,333	—	27	—	—	—	—	—	—	27
Issuance of common stock at $2.10 per share for services	—	—	540	—	1	—	—	—	—	—	—	1
Net loss	—	—	—	—	—	—	—	—	—	—	(619)	(619)
Balance at December 31, 1994	834,375	834	122,206	—	93	—	—	—	—	—	(1,211)	(284)
Issuance of Series A preferred stock at $1.00 per share for cash	1,128,531	1,129	—	—	—	—	—	—	—	—	—	1,129
Issuance of Series B preferred stock at $2.75 per share for cash and in exchange for outstanding note payable, net of issuance costs of $15,548	1,955,555	5,362	—	—	—	—	—	—	—	—	—	5,362
Net loss	—	—	—	—	—	—	—	—	—	—	(887)	(887)
Balance at December 31, 1995	3,918,461	7,325	122,206	—	93	—	—	—	—	—	(2,098)	5,320
Issuance of common stock upon exercise of options	—	—	4,445	—	9	—	—	—	—	—	—	9
Net loss	—	—	—	—	—	—	—	—	—	—	(3,025)	(3,025)
Balance at December 31, 1996	3,918,461	7,325	126,651	—	102	—	—	—	—	—	(5,123)	2,304
Issuance of Series C preferred stock at $5.63 per share for cash, net of issuance costs of $66,735	947,295	5,267	—	—	—	—	—	—	—	—	—	5,267
Issuance of common stock upon exercise of options	—	—	5,186	—	11	—	—	—	—	—	—	11
Repurchase and retirement of Series A preferred stock	(11,153)	(11)	—	—	—	—	—	—	—	—	(45)	(56)
Net loss	—	—	—	—	—	—	—	—	—	—	(6,752)	(6,752)
Balance at December 31, 1997	4,854,603	12,581	131,837	—	113	—	—	—	—	—	(11,920)	774
Issuance of Series C preferred stock and warrants at $5.63 per share in exchange for conversion of bridge loans of $1,000,000 and cash, net of issuance costs of $43,676	844,166	4,709	—	—	—	—	—	—	—	—	—	4,709
Preferred and common stock subscribed	—	—	—	—	—	—	1,266	(1,266)	—	—	—	—
Issuance of common stock for exercisable options	—	—	2,192	—	6	—	—	—	—	—	—	6
Issuance of common stock at $7.60 per share for cash	—	—	9,388	—	71	—	—	—	—	—	—	71
Deferred compensation related to stock options	—	—	—	—	12	—	—	—	(12)	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—	—	—	11	—	—	11
Net loss	—	—	—	—	—	—	—	—	—	—	(9,624)	(9,624)
Balance at December 31, 1998	5,698,769	17,290	143,417	—	202	—	1,266	(1,266)	(1)	—	(21,544)	(4,053)
Issuance of Series C preferred stock and warrants at $5.63 per share in exchange for conversion of bridge loans and cash, net of issuance costs of $41,929	1,235,894	6,959	—	—	—	—	—	—	—	—	—	6,959
Issuance of preferred and common stock subscribed	221,551	1,247	2,464	—	19	—	(1,266)	1,266	—	—	—	1,266
Issuance of common stock for exercisable options	—	—	20,610	—	93	—	—	—	—	—	—	93
Issuance of common stock at $7.60 per share for cash	—	—	5,212	—	39	—	—	—	—	—	—	39
Deferred compensation related to stock options	—	—	—	—	3,538	—	—	—	(3,538)	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—	—	—	1,324	—	—	1,324
Net loss	—	—	—	—	—	—	—	—	—	—	(14,284)	(14,284)
Balance at December 31, 1999	7,156,214	25,496	171,703	—	3,891	—	—	—	(2,215)	—	(35,828)	(8,656)

ISTA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
PERIOD FROM FEBRUARY 13, 1992 (INCEPTION) TO DECEMBER 31, 2003 (CONTINUED)
(in thousands, except share and per share data)

	Convertible Preferred Stock		Common Stock		Additional Paid-in	Preferred and Common Stock Subscribed		Subscriptions	Deferred	Accumulated Other	Deficit Accumulated During the	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Shares	Amount	Receivable	Compensation	Comprehensive Income	Development Stage	Equity (Deficit)
Issuance of Series C preferred stock at 11.70 per share for acquisition of Visionex	3,319,363	28,773	—	—	—	—	—	—	—	—	—	28,773
Issuance of Series D preferred stock at $5.63 per share	1,776,199	10,000	—	—	—	—	—	—	—	—	—	10,000
Issuance of common stock in conjunction with the initial public offering, net of issuance costs of $4,479	—	—	345,000	—	31,746	—	—	—	—	—	—	31,746
Conversion of Preferred Stock to common stock	(12,251,776)	(64,269)	878,367	2	64,267	—	—	—	—	—	—	
Issuance of Common Stock from exercise of warrants	—	—	79,702	—	41	—	—	—	—	—	—	41
Issuance of common stock for options	—	—	67,066	—	362	—	—	—	—	—	—	362
Common stock issued for services	—	—	—	—	113	—	—	—	—	—	—	113
Deferred compensation related to stock options	—	—	—	—	3,535	—	—	—	(3,535)	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—	—	—	3,165	—	—	3,165
Deemed dividend for preferred stockholders	—	—	—	—	—	—	—	—	—	—	(19,245)	(19,245)
Net loss	—	—	—	—	—	—	—	—	—	—	(21,857)	(21,857)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(27)	—	(27)
Unrealized gain on investments	—	—	—	—	—	—	—	—	—	149	—	149
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	(21,735)
Balance at December 31, 2000	—	—	1,541,838	2	103,955	—	—	—	(2,585)	122	(76,930)	24,564
Issuance of common stock for options	—	—	17,417	—	79	—	—	—	—	—	—	79
Common stock issued for cash	—	—	84,567	—	3,999	—	—	—	—	—	—	3,999
Common stock issued under ESPP	—	—	699	—	25	—	—	—	—	—	—	25
Common stock issuable under ESPP	—	—	800	—	22	—	—	—	—	—	—	22
Deferred compensation related to stock options	—	—	—	—	2,960	—	—	—	(2,960)	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—	—	—	1,902	—	—	1,902
Net loss	—	—	—	—	—	—	—	—	—	—	(22,507)	(22,507)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(14)	—	(14)
Unrealized loss on investments	—	—	—	—	—	—	—	—	—	(130)	—	(130)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	(22,651)
Balance at December 31, 2001	—	—	1,645,321	2	111,040	—	—	—	(3,643)	(22)	(99,437)	7,940
Issuance of common stock for options	—	—	32,008	—	121	—	—	—	—	—	—	121
Common stock issued under ESPP	—	—	3,531	—	26	—	—	—	—	—	—	26
Common stock issued for services	—	—	30,000	—	197	—	—	—	—	—	—	197
Issuance of common stock in conjunction with the private placement, net of issuance costs of $2,657	—	—	11,578,926	11	41,332	—	—	—	—	—	—	41,343
Repurchase of common stock	—	—	(1,666)	—	(13)	—	—	—	—	—	—	(13)
Deferred compensation related to stock options	—	—	—	—	(93)	—	—	—	93	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—	—	—	2,160	—	—	2,160
Amortization of fair value of warrant discount	—	—	—	—	412	—	—	—	—	—	—	412
Net loss	—	—	—	—	—	—	—	—	—	—	(22,957)	(22,957)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	15	—	15
Unrealized loss on investments	—	—	—	—	—	—	—	—	—	(16)	—	(16)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	(22,958)
Balance at December 31, 2002	—	—	13,288,120	13	153,022	—	—	—	(1,390)	(23)	(122,394)	29,228
Issuance of common stock for options	—	—	79,857	—	301	—	—	—	—	—	—	301
Common stock issued under ESPP	—	—	7,462	—	20	—	—	—	—	—	—	20
Common stock issued for services	—	—	—	—	—	—	—	—	—	—	—	—
Issuance of common stock in conjunction with the follow-on public offering, net of issuance costs of $2,831	—	—	4,000,000	4	35,165	—	—	—	—	—	—	35,169
Repurchase of common stock	—	—	—	—	—	—	—	—	—	—	—	—
Deferred compensation related to stock options	—	—	—	—	110	—	—	—	(110)	—	—	—
Amortization of deferred compensation	—	—	—	—	3	—	—	—	953	—	—	956
Amortization of fair value of warrant discount	—	—	—	—	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	—	—	—	—	(25,245)	(25,245)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(2)	—	(2)
Unrealized loss on investments	—	—	—	—	—	—	—	—	—	(3)	—	(3)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	(25,250)
Balance at December 31, 2003	—	$ —	17,375,439	$ 17	$ 188,621	—	$ —	$ —	$ (547)	$ (28)	$ (147,639)	$ 40,424

See accompanying notes.

ISTA PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Years Ended December 31,			For the Period From February 13, 1992 (Inception) To December 31,
	2003	2002	2001	2003
OPERATING ACTIVITIES				
Net loss	$ (25,245)	$ (22,957)	$ (22,507)	$ (128,349)
Adjustments to reconcile net loss to net cash used in operating activities:				
Amortization of deferred compensation	956	2,160	1,902	9,527
Amortization of fair value of warrant discount and related accrued interest	—	467	—	467
Common stock issued for services	—	197	—	310
Forgiveness of note receivable	—	—	162	162
Depreciation and amortization	343	337	344	2,009
Changes in operating assets and liabilities:				
Advanced payments — clinical trials and other current assets	(526)	(18)	611	(1,035)
Note receivable from officer	—	—	—	(162)
Accounts payable	1,162	20	285	2,073
Accrued compensation and related expenses	12	(112)	435	699
Accrued expenses — clinical trials and other accrued expenses	956	(746)	(136)	2,658
Deferred rent	(1)	8	(10)	9
Deferred income	(278)	(278)	5,000	4,444
License fee received from Visionex	—	—	—	5,000
Net cash used in operating activities	(22,621)	(20,922)	(13,914)	(102,188)
INVESTING ACTIVITIES				
Purchases of marketable securities	(37,036)	(14,517)	(12,346)	(83,707)
Maturities of marketable securities	9,009	14,280	25,919	52,199
Purchase of equipment	(113)	(402)	(251)	(2,655)
Proceeds from refinancing under capital leases	—	—	—	827
Deposits and other assets	—	(9)	72	(53)
Cash acquired from Visionex transaction	—	—	—	4,403
Net cash (used in) provided by investing activities	(28,140)	(648)	13,394	(28,986)
FINANCING ACTIVITIES				
Payments on obligation under capital leases	—	—	(15)	(827)
Proceeds from exercise of stock options	301	121	79	982
Proceeds from exercise of warrants	—	—	—	41
Proceeds from bridge loans with related parties	—	—	—	5,047
Payments on bridge loans with related parties	—	—	—	(3,755)
Proceeds from issuance of preferred stock	—	—	—	34,215
Repurchase of preferred stock	—	—	—	(56)
Proceeds from issuance of common stock and conversion of note payable, net of issuance costs	35,189	41,343	4,046	112,539
Net cash provided by financing activities	35,490	41,464	4,110	148,186
Effect of exchange rate changes on cash	2	15	(14)	(24)
(Decrease) / Increase in cash and cash equivalents	(15,269)	19,909	3,576	16,988
Cash and cash equivalents at beginning of period	32,257	12,348	8,772	—
Cash and cash equivalents at end of period	$ 16,988	$ 32,257	$ 12,348	$ 16,988
SUPPLEMENTAL DISCLOSURE OF CASH FLOW INFORMATION:				
Cash paid during the period for interest	$ 10	$ 6	$ 25	$ 318
SUPPLEMENTAL SCHEDULE OF NONCASH INVESTING AND FINANCING ACTIVITIES:				
Preferred stock issued in exchange for bridge loans with stockholders and accrued interest	$ —	$ —	$ —	$ 2,357
Extinguishment of liability through acquisition of Visionex	$ —	$ —	$ —	$ 5,000
Series C preferred stock issued for acquisition of Visionex	$ —	$ —	$ —	$ 28,773
Conversion of preferred stock to common stock	$ —	$ —	$ —	$ 64,269

See accompanying notes.

1. Organization and Summary of Significant Accounting Policies

The Company

ISTA Pharmaceuticals, Inc. ("ISTA" or the "Company") was incorporated in the state of California on February 13, 1992 to discover, develop and market new remedies for diseases and conditions of the eye. The Company reincorporated in Delaware on August 4, 2000.

ISTA is an emerging specialty pharmaceutical company focused on the development and commercialization of unique and uniquely improved products for serious diseases and conditions of the eye. Since the Company's inception, it has devoted its resources primarily to fund research and development programs and late-stage product acquisitions. In December 2001, ISTA announced its strategic plan to transition from a development-stage organization to a specialty pharmaceutical company with a primary focus on ophthalmology.

On March 8, 2000, ISTA acquired all the outstanding shares of Visionex in a transaction accounted for as a purchase (see Note 9). The operations of Visionex are included in the consolidated financial statements since the date of acquisition. All intercompany accounts have been eliminated in consolidation.

Basis of Presentation

The accompanying financial statements have been prepared assuming that the Company will continue as a going concern. This basis of accounting contemplates the recovery of the Company's assets and the satisfaction of its liabilities in the normal course of business. Since inception, the Company has been primarily engaged in research and development, and through December 31, 2003, the Company has incurred accumulated losses of $147.6 million, which includes the deemed dividend to preferred stockholders of $19.2 million (Note 9). The Company's ability to transition from the development stage and ultimately, to attain profitable operations, is dependent upon obtaining sufficient working capital to complete the successful development of its products, FDA approval of its products, achieving market acceptance of such products and achievement of sufficient levels of revenue to support the Company's cost structure. Management believes that the Company's existing capital resources will enable the Company to fund operations for at least the next 12 months.

On November 11, 2002, the stockholders approved a 1-for-10 reverse stock split. The reverse stock split reduced the outstanding number of shares but not the par value of the Company's common stock. The stated capital on the Company's balance sheet attributable to the outstanding shares of common stock (which is determined by multiplying the par value by the number of shares outstanding) was reduced proportionately based on the reverse stock split ratio of 1-for-10. However, the additional paid-in capital account on the Company's balance sheet was increased by the amount by which the stated capital was reduced, so that the aggregate amount of the Company's stockholders' equity is unchanged by the reverse stock split. The per share net loss and the per share net book value of the Company's common stock is also increased because there are fewer shares of common stock outstanding. All historical common stock shares and per share data have been adjusted for the reverse stock split throughout these financial statements for all periods presented.

Cash and Cash Equivalents

Cash and cash equivalents consist of cash in banks, certificates of deposit and short-term investments with original maturities of three months or less when purchased. Cash and cash equivalents are carried at cost, which management believes approximates fair value because of the short-term maturity of these instruments.

Short-term Investments

Investments with an original maturity of more than three months from the date of purchase are considered short-term investments and have been classified by management as available-for-sale. Such investments are carried at fair value, with unrealized gains and losses included as a separate component of stockholders' equity. The basis for computing realized gain or losses is by specific identification.

Fair Value of Financial Instruments

The carrying amount of cash and cash equivalents, short-term investments, accounts receivable, accounts payable and accrued liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash and cash equivalents and short-term investments.

Property and Equipment

Property and equipment are recorded at cost. Equipment and furniture are depreciated using the straight-line method over their estimated useful lives (generally three to seven years) and leasehold improvements are amortized using the straight-line method over the estimated useful life of the asset or the lease term, whichever is shorter. Equipment acquired under capital leases is amortized over the estimated useful life of the assets. The Company has no capital leases for the year ended December 31, 2003.

Impairment of Long-lived Assets

In accordance with Statement of Financial Accounting Standards ("SFAS") No. 144, "Accounting for the Impairment or Disposal of Long-Lived Assets", if indicators of impairment exist, the Company assesses the recoverability of the affected long-lived assets by determining whether the carrying value of such assets can be recovered through undiscounted future operating cash flows. If impairment is indicated, the Company measures the amount of such impairment by comparing the fair value to the carrying value. While the Company's current and historical operating and cash flow losses are indicators of impairment, the Company believes the future cash flows to be received from the long-lived assets will exceed the assets' carrying value, and accordingly, the Company has not recognized any impairment losses through December 31, 2003.

Research and Development Costs

Expenditures relating to research and development are expensed in the period incurred. The Company also expenses costs incurred to obtain and prosecute patents, as recoverability of such expenditures is not assured. Approximately $251,000, $211,000 and $204,000 of patent-related costs were included in research and development expense in 2003, 2002 and 2001, respectively. From February 13, 1992 (inception) through December 31, 2003 the Company expensed approximately $1,506,000 related to these costs.

Our research and development expenses to date have consisted primarily of costs associated with the clinical trials of our product candidates, compensation and other expenses for research and development personnel, costs for consultants and contract research, costs related to development of commercial scale manufacturing capabilities for our product candidates Vitrase®, Istalol™ and Xibrom™ and in process research and development costs related to the acquisition of three late-stage development compounds.

We generally classify and separate research and development expenditures into amounts related to preclinical research, clinical development and manufacturing development. We have not tracked our historical research and development costs by specific project, rather, we track costs by the type of cost incurred.

Stock-based Compensation

As permitted by SFAS No. 123, "Accounting for Stock-Based Compensation", the Company has elected to follow Accounting Principals Board ("APB") Opinion No. 25, "Accounting for Stock Issued to Employees", and related interpretations in accounting for stock-based employee compensation. Under APB 25, if the exercise price of the Company's employee and director stock options equals or exceeds the estimated fair value of the underlying stock on the date of grant, no compensation expense is recognized.

When the exercise price of the employee or director stock options is less than the estimated fair value of the underlying stock on the grant date, the Company records deferred compensation for the difference and amortizes this amount to expense in accordance with Financial Accounting Standards Board ("FASB") Interpretation No. 28, "Accounting for Stock Appreciation Rights and Other Variable Stock Option or Award Plans", over the vesting period of the options.

Options or stock awards issued to non-employees are recorded at their fair value as determined in accordance with SFAS No. 123 and Emerging Issues Task Force ("EITF") No. 96-18, "Accounting for Equity Instruments That Are Issued to

Other Than Employees for Acquiring or in Conjunction With Selling Goods or Services", and recognized over the related service period. Deferred charges for options granted to non-employees are periodically re-measured as the options vest.

As required under SFAS No. 123, "Accounting for Stock-Based Compensation", and SFAS No. 148, "Accounting for Stock-Based Compensation Transition and Disclosure", the pro forma effects of stock-based compensation on net loss have been estimated at the date of grant using the Black-Scholes option-pricing model. The Black-Scholes option valuation model was developed for use in estimating the fair value of traded options that have no vesting restrictions and are fully transferable. In addition, option valuation models require the input of highly subjective assumptions including the expected stock price volatility. Because the Company's employee stock options have characteristics significantly different from those of traded options, and because changes in the subjective input assumptions can materially affect the fair value estimate, in management's opinion, the existing models do not necessarily provide a reliable single measure of the fair value of its employee stock options.

In December 2002, the FASB issued SFAS No. 148, "Accounting for Stock-Based Compensation—Transition and Disclosure." SFAS No. 148 is an amendment to SFAS No. 123 providing alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation and also provides additional disclosures about the method of accounting for stock-based employee compensation. Amendments are effective for financial statements for the Company beginning January 1, 2003. The Company has currently chosen to not adopt the voluntary change to the fair value based method of accounting for stock-based employee compensation. If the Company should choose to adopt such a method, its implementation pursuant to SFAS No. 148 could have a material effect on the Company's consolidated financial position and results of operations.

The fair value of these options was estimated at the date of grant using the minimum value pricing model for grants prior to the initial public offering and the Black Scholes method for grants after the initial public offering with the following weighted average assumptions for 2003, 2002 and 2001: risk-free interest rate of 3.0%, 3.0% and 5.1%, respectively, zero dividend yield, volatility of 73% in 2003, 2002 and 2001; and a weighted-average life of the option of four years. The estimated weighted average fair value of stock options granted during 2003, 2002 and 2001 was $2.99, $3.15 and $23.10, respectively.

For purposes of pro forma disclosures, the estimated fair value of the options is amortized to expense over the vesting period of the related options. The Company's pro forma information follows (in thousands, except per share data):

	Years Ended December 31,		
	2003	2002	2001
Net loss attributable to common stockholders, as reported	$ (25,245)	$ (22,957)	$ (22,507)
Add: Stock-based employee compensation expense included in net loss attributable to commons shareholders	956	2,160	1,902
Deduct: Total stock-based employee compensation expense determined under fair value based method for all awards	(1,604)	(718)	(1,882)
Pro forma net loss	$ (25,893)	$ (21,515)	$ (22,487)
Net loss per share, basic and diluted, as reported	$ (1.83)	$ (7.53)	$ (14.43)
Pro forma net loss per share, basic and diluted	$ (1.88)	$ (7.06)	$ (14.42)

Use of Estimates

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

Revenue Recognition

We recognize revenue consistent with the provisions of the Securities and Exchange Commission's ("SEC") Staff Accounting Bulletin No. 101 ("SAB 101"), "Revenue Recognition", which sets forth guidelines in the timing of revenue recognition based upon factors such as passage of title, installation, payments and customer acceptance. Amounts received for upfront product and technology license fees under multiple-element arrangements are deferred and recognized over the period of such services or performance if such arrangements require on-going services or performance. Non-refundable amounts received for milestone payments are recognized upon (i) the achievement of specified milestones when the Company has earned the milestone payment or, (ii) the milestone payment is substantive in nature and the achievement of the milestone was not reasonably assured at the inception of the agreement. The Company defers payments for milestone events which are reasonably assured and recognizes them ratably over the minimum remaining period of the Company's performance obligations. Payments for milestones which are not reasonably assured are treated as the culmination of a

separate earnings process and are recognized as revenue when the milestones are achieved. Royalty revenue will be recognized upon sale of the related products, provided the royalty amounts are fixed and determinable and collection of the related receivable is probable. Any amounts received prior to satisfying our revenue recognition criteria will be recorded as deferred revenue in the accompanying balance sheets.

Net Loss Per Share

In accordance with SFAS No. 128, "Earnings Per Share", and SEC Staff Accounting Bulletin No. 98, basic net income (loss) per common share is computed by dividing the net income (loss) for the period by the weighted average number of common shares outstanding during the period. Diluted net income (loss) per share is computed by dividing the net income (loss) for the period by the weighted average number of common and common equivalent shares outstanding during the period.

The Company has excluded all outstanding options and warrants, and shares subject to repurchase from the calculation of diluted loss per common share because all such securities are anti-dilutive for all periods presented. The total number of shares excluded from the calculation of diluted net loss per share, prior to application of the treasury stock method for options and warrants, was 823,988, 2,071,864 and 355,664 for the years ended December 31, 2003, 2002 and 2001, respectively.

Segment Reporting

The Company currently operates in only one segment.

Comprehensive Income

The Company has adopted the provisions of SFAS No. 130, "Reporting Comprehensive Income", which establishes standards for reporting comprehensive income and its components in financial statements. Comprehensive income, as defined, includes all changes in equity (net assets) during a period from non-owner sources. Net loss and other comprehensive loss, including foreign currency translation adjustment and unrealized gains and losses on investments shall be reported, net of their related tax effect, to arrive at comprehensive loss.

As of December 31, 2003, accumulated foreign currency translation adjustment and accumulated unrealized gain on investments were ($25,000) and ($3,000), respectively.

Reclassifications

Certain amounts in the prior year financial statements have been reclassified to conform to the current year presentation.

2. Balance Sheet Details

Property and Equipment

Equipment and leasehold improvements and related accumulated depreciation and amortization are as follows (in thousands):

	December 31,	
	2003	2002
Property and equipment:		
Equipment	$ 1,660	$ 1,561
Furniture and fixtures	460	452
Leasehold improvements	314	308
	2,434	2,321
Less accumulated depreciation and amortization	(1,785)	(1,442)
	$ 649	$ 879

Total depreciation and amortization expense amounted to $343,000, $337,000 and $344,000 and $2,009,000 for the years ended December 31, 2003, 2002 and 2001 and for the period from February 13, 1992 (inception) to December 31, 2003, respectively.

Accrued Expenses

Other accrued expenses consist of the following (in thousands):

	December 31, 2003	December 31, 2002
Accrued general expenses	$ 761	$ 618
Accrued contract manufacturing expenses	1,268	216
Accrued state tax payable	29	23
	$ 2,058	$ 857

3. Short-Term Investments

The Company classifies its short-term investments as "available-for-sale" and records such assets at the estimated fair value with unrealized gains and losses excluded from earnings and reported in comprehensive income (loss). The basis for computing realized gains or losses is by specific identification.

The following is a summary of available-for-sale securities (in thousands):

	Gross Amortized Cost	Net Unrealized Gains/(Losses)	Estimated Fair Value
At December 31, 2003:			
U.S. Treasury securities and agency bonds	$ 15,097	$ 15	$ 15,112
Corporate Bonds	7,131	(18)	7,113
Auction Rate securities	9,250	0	9,250
	$ 31,478	$ (3)	$ 31,475

	Gross Amortized Cost	Net Unrealized Gains/(Losses)	Estimated Fair Value
At December 31, 2002:			
U.S. Treasury securities and agency bonds	$ 3,451	$ 4	$ 3,455
	$ 3,451	$ 4	$ 3,455

Available-for-sale securities by contractual maturity are as follows (in thousands):

Due in one year or less	$ 20,659
Due after one year through two years	10,816
	$ 31,475

Realized gains and losses were immaterial to the Company's financial results for the years ended December 31, 2003 and 2002. Gross unrealized gains were $37,000, $7,000 and $20,000 and $221,000 for December 31, 2003, 2002 and 2001 and for the period from February 13, 1992 (inception) to December 31, 2003, respectively. Gross unrealized losses were $44,000, $23,000 and $1,000 and $76,000 for the years ended December 31, 2003, 2002 and 2001 and for the period from February 13, 1992 (inception) to December 31, 2003, respectively.

4. Related Party Transactions

During the years ended December 31, 2003, 2002 and 2001 and the period from February 13, 1992 (inception) to December 31, 2003, the Company made total payments of approximately $0, $6,000 and $7,000 and $198,000, respectively, to a management company owned by a stockholder of the Company for reimbursement of services performed on behalf of the Company.

5. Stockholders' Equity

Common and Preferred Stock

During 2000, the Company issued 3,319,363 shares of Series C preferred stock at $11.70 per share to acquire all the outstanding capital stock of Visionex, which was convertible into 245,879 shares of common stock (see Note 9).

Also during 2000, the Company issued 1,776,199 shares of Series D preferred stock at $5.63 per share to Allergan for proceeds of $10.0 million (see Note 10).

On August 25, 2000, the Company closed on its initial public offering with the sale of 300,000 shares of common stock. On September 12, 2000, the underwriters of the Company's initial public offering exercised their over allotment to purchase an additional 45,000 shares. The net proceeds from the initial public offering totaled $31.7 million. The Series A, B

and C preferred stock converted on a one to 7.4 basis into 775,961 shares of common stock and the Series D preferred stock converted into 102,406 shares of common stock.

On December 13, 2001, the Company sold, in a private placement, 84,567 shares of common stock to Otsuka Pharmaceuticals, Co. Ltd. for $4.0 million (see Note 11).

On November 19, 2002, the Company sold, in a private placement, 10,526,306 shares of common stock to certain investors for $40.0 million. Additionally, $4.0 million of promissory notes were converted to 1,052,620 shares of common stock to several of the same investors.

On November 12, 2003, the Company sold, in a follow-on public offering, 4,000,000 shares of common stock to certain investors for $38.0 million.

At December 31, 2003 and 2002, the Company had 5,000,000 shares of preferred stock authorized at a $.001 par value and no shares were issued and outstanding.

Preferred and Common Stock Subscribed

Preferred and common stock subscribed at December 31, 1998, reflected 221,551 and 2,464 shares of the Company's Series C preferred and common stock, respectively, subscribed by certain stockholders in December 1998 at a per share price of $5.63 and $7.60, respectively. A corresponding subscription receivable was included in stockholders' equity as of December 31, 1998. In January 1999, the Company completed the subscribed transaction, and all preferred and common stock subscription amounts were received and all preferred and common stock and common stock warrants subject to the subscriptions were issued. The common stock warrants were not separately valued; therefore the entire proceeds from the transaction were included in preferred stock in the accompanying balance sheet.

Common Stock Warrants

In connection with the Series C preferred stock financing completed during 1998 and 1999, the Company also sold to the investors warrants to purchase 85,472 shares of common stock, which were bundled with the preferred stock as a combined unit. Each of the combined units consists of 10 shares of preferred stock and five warrants to purchase .01 shares of common stock at $0.76 per share. The warrants expire upon the earlier of five years from the date of issuance or the closing of an initial public offering. The warrants also provide the holder with the option to receive common shares equal to the intrinsic value of the warrant at the time of warrant exercise (a "cashless exercise"). As the warrants were sold with the stock in a combined unit, the warrants were not separately valued and the proceeds from the financing were not allocated between Series C Preferred Stock and common stock. Accordingly, the entire proceeds from the financing are included in preferred stock in the accompanying balance sheet. In connection with the Company's initial public offering in August 2000, all of the warrants were exercised for the purchase of shares of common stock. A total of 80,150 warrants were used to purchase 74,379 shares of common stock in a cashless exercise and 5,323 warrants were used to purchase 5,323 shares of common stock in a cash exercise.

In November 2002, the Company consummated a private placement of $40.0 million of its common stock and warrants exercisable for an additional $6.0 million of common stock to certain investors with a purchase price of $3.80 per share. In addition, $4.0 million of promissory notes previously issued to several of the same investors in the Company's September 2002 bridge financing were converted into 1,052,620 shares of the Company's common stock, based upon the conversion price of $3.80 per share, concurrently with the consummation of the private placement.

The warrants were accounted for under EITF 98-5 "Accounting for Convertible Securities with Beneficial Conversion Features or Contingently Adjustable Conversion Ratios", and APB 14, "Accounting for Convertible Debt and Debt Issued with Stock Purchase Warrants", which require the warrants to be recorded at their fair value as a discount on the underlying note. The fair value of the warrants was determined to be $412,000 under SFAS No. 123, "Accounting for Stock-Based Compensation", using the Black-Scholes Valuation Model. The warrants were valued using the following assumptions: risk-free interest rate of 3%; dividend yield of 0%; expected volatility of 73%; and a term of five years. The value of the warrants was amortized as interest expense over the period of time the promissory notes were outstanding in 2002.

Employee Stock Purchase Plan

In April 2000, the Company's Board of Directors adopted the Employee Stock Purchase Plan (the "Stock Purchase Plan"), which initially provides for the issuance of a maximum of 20,000 shares of common stock.

Eligible employees can have up to 15% of their earnings withheld, subject to certain maximums, to be used to purchase shares of the Company's common stock every January and July. The price of the common stock purchased under the Stock

Purchase Plan will be equal to 85% of the lower of the fair value of the common stock on the commencement date of the offering period or the specified purchase date. As of December 31, 2003, 7,462 shares had been issued to participants, with an additional 4,069 shares issuable at year end.

The Stock Purchase Plan provides for annual increases in the number of shares available for issuance under the plan on the first day of each year, beginning in 2001, equal to the lesser of 20,000 shares, 1.5% of the outstanding shares of common stock on the first day of the year, or a lesser amount as the Board of Directors may determine. As of January 1, 2003, the number of shares available for issuance increases to 200,000 shares, 1.5% of the outstanding shares of common stock on the first day of the year, or a lesser amount as the Board of Directors may determine.

Stock Compensation Plan

The Company had reserved 53,618 shares of common stock under the 1993 Stock Plan (the "Plan") for issuance to eligible employees, officers, directors and consultants. The Plan provided for the grant of incentive and nonstatutory stock options. Terms of the stock option agreements, including vesting requirements, were determined by the Board of Directors, subject to the provisions of the Plan. Options granted by the Company vest ratably over four years and are exercisable from the date of grant for a period of ten years. The option price equaled the estimated fair value of the common stock as determined by the Board of Directors on the date of the grant. Upon completion of the Company's initial public offering in August 2000, the 1993 Stock Plan was terminated. No further option grants will be made under this Plan, and any shares reserved but not yet issued and cancellations under the 1993 Stock Plan will be made available for grant under the 2000 Stock Plan.

In 2000, the Company's stockholders approved the 2000 Stock Plan (the "2000 Stock Plan") that became effective upon the completion of the Company's initial public offering in August 2000. The 2000 Stock Plan provides for the grant of incentive stock options to employees and for the grant of nonstatutory stock options and stock purchase rights to employees, directors and consultants. A total of 20,000 shares of common stock were initially reserved for issuance under the 2000 Stock Plan. The 2000 Stock Plan provides for annual increases in the number of shares available for issuance under the plan on the first day of each year, beginning in 2000, equal to the lesser of 20,000 shares, 1.5% of the outstanding shares of common stock on the first day of the year, or a lesser amount as the Board of Directors may determine. As of January 1, 2003, the number of shares available for issuance increases to 200,000 shares, 1.5% of the outstanding shares of common stock on the first day of the year, or a lesser amount as the Board of Directors may determine. At the Special Shareholder Meeting on November 11, 2002, the shareholders approved an increase of 2,500,000 options available for issuance under the 2000 Stock Plan.

As of December 31, 2003, a total of 710,129 shares of common stock were reserved for issuance under the 2000 Stock Plan.

In December 2001, the Board of Directors granted our new Chief Executive Officer and President a stand-alone option agreement to purchase 100,461 shares of common stock of the Company for a purchase price of $20.00 per share.

In June 2002, the Board of Directors granted our new Vice President, Sales & Marketing a stand-alone option agreement to purchase 30,000 shares of common stock of the Company for a purchase price of $8.50.

In August 2002, the Board of Directors granted our new Vice President, Operations a stand-alone option agreement to purchase 15,000 shares of common stock of the Company for a purchase price of $6.90.

A summary of the Company's stock option activity and related information follows:

	Shares	Price Per Share	Weighted-Average Exercise Price
Outstanding at December 31, 2000	223,619	$ 2.03 – $104.00	$ 16.92
Granted	174,275	$19.00 – $ 51.25	$ 26.28
Exercised	(17,417)	$ 2.03 – $ 7.56	$ 5.09
Canceled	(25,314)	$ 7.56 – $104.00	$ 68.15
Outstanding at December 31, 2001	355,163	$ 2.03 – $104.00	$ 17.35
Granted	1,773,670	$ 3.49 – $ 16.10	$ 3.80
Exercised	(32,008)	$ 2.03 – $ 7.56	$ 3.74
Canceled	(24,961)	$ 7.56 – $104.00	$ 42.61
Outstanding at December 31, 2002	2,071,864	$ 2.03 – $ 51.25	$ 5.66
Granted	536,150	$ 4.20 – $ 9.05	$ 5.84
Exercised	(79,857)	$ 2.03 – $ 7.56	$ 3.78
Canceled	(219,541)	$ 3.49 – $ 51.25	$ 9.82
Outstanding at December 31, 2003	2,308,616	$ 3.49 – $ 51.25	$ 5.37

The following table summarizes information about options outstanding at December 31, 2003:

	Options Outstanding			Options Exercisable	
Range of Exercise Price	Number Outstanding	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable and Vested	Weighted Average Exercise Price
$3.49 – $5.40	1,851,685	8.99	$ 3.75	480,115	$ 3.51
$6.85—$9.70	310,419	9.16	$ 7.25	64,904	$ 7.62
$16.10 – $51.25	146,512	7.60	$ 21.91	74,981	$ 22.55
$3.49 –$51.25	2,308,616	8.92	$ 5.37	620,000	$ 6.24

Shares Reserved for Future Issuance

The following shares of common stock are reserved for future issuance at December 31, 2003:

Stock plans:	
Options granted and outstanding	2,308,616
Reserved for future option grants	710,129
	3,018,745
Warrants:	
Reserved for future issuance	1,842,104
Stock purchase plan:	
Reserved for future issuance	43,426
	4,904,275

Deferred Compensation

During the years ended December 31, 2003, 2002 and 2001 in connection with the grant of various stock options to employees, the Company recorded deferred stock compensation totaling $110,000, $93,000 and $2,960,000, respectively, representing the difference between the exercise price and the estimated market value of the Company's common stock as determined by the Company's management on the date such stock options were granted. Deferred compensation is included as a reduction of stockholders' equity and is being amortized to expense over the vesting period of the options in accordance with FASB Interpretation No. 28, which permits an accelerated amortization methodology. During the years ended December 31, 2003, 2002 and 2001, the Company recorded amortization of deferred compensation expense of $956,000, $2,160,000 and $1,902,000, respectively. As of December 31, 2003, total charges to be recognized in future periods from amortization of deferred stock compensation are anticipated to be approximately $423,000, $124,000 and $11,000 for the years ending December 31, 2004, 2005 and 2006, respectively.

In August 2001, the Company offered certain employees an opportunity to exchange certain of their existing stock options. These options are required to be accounted for as variable stock options in accordance with FIN 44. Variable stock options can result in significant increases and decreases in compensation expense subject to the variability of the Company's stock price. There was no material impact on the financial statements in 2003 or 2002 as a result of the variable stock options.

6. Commitments and Contingencies

Clinical Trial Agreements

During 1998 and 1999, the Company entered into several agreements with contract research organizations to perform Phase III clinical trials in various countries. Upon early termination, the Company is subject to a termination fee of approximately $200,000 as defined in the agreements. The Company presently has no intention of terminating the agreements. As of December 31, 2003, the Company had approximately $974,000 of future obligations relating to services to be provided under these agreements.

Lease Commitments

The Company leases its corporate and laboratory facilities and certain equipment under various operating leases. As of December 31, 2003, the Company has made approximately $31,000 in cash deposits related to operating leases. Provisions of the facilities lease provide for abatement of rent during certain periods and escalating rent payments during the term. For financial reporting purposes, rent expense is recognized on a straight-line basis over the term of the lease. Accordingly, rent expense recognized in excess of rent paid is reflected as deferred rent. Additionally, the Company is required to pay taxes, insurance and maintenance expenses related to the building. Rent expense on the facilities and equipment during 2003, 2002 and 2001 and the period from February 13, 1992 (inception) to December 31, 2003 was $512,000, $452,000 and $313,000 and $2,679,000, respectively.

Future annual minimum payments under operating leases as of December 31, 2003, are as follows (in thousands):

Years Ending December 31:	
2004	$ 351
2005	135
2006	59
2007	49
2008	45
	$ 639

7. Income Taxes

At December 31, 2003, the Company had federal and California income tax net operating loss carryforwards of approximately $95,549,000 and $84,381,000, respectively.

Our federal tax loss carryforwards will begin to expire in 2008, unless previously utilized. Our California tax loss carryforwards will begin to expire in 2004, unless previously utilized. We also have federal and California research tax credit carryforwards of approximately $4.6 million and $2.6 million, respectively. The federal research tax credits will begin to expire in 2010, unless previously utilized. Our California research tax credit carryforwards do not expire and will carryforward indefinitely until utilized. In addition, we have California manufacturers investment credit of approximately $30,000 that will begin to expire in 2010, unless previously utilized.

Pursuant to Sections 382 and 383 of the Internal Revenue Code ("IRC"), annual use of the Company's net operating losses and tax credit carryforwards may be limited because of cumulative changes in ownership of more than 50% that have occurred. During 2002, a change in ownership as described in IRC Section 382, did occur and will limit the ability of the Company to utilize the net operating losses and tax credit carryforwards in the future.

Significant components of the Company's deferred tax assets are shown below. A valuation allowance of $54,669,000 has been established to offset the deferred tax assets, as realization of such assets is uncertain.

	December 31,	
	2002	2001
Deferred tax asset:		
Net operating loss carryforwards	$ 40,902,000	$ 29,307,000
Tax credits	7,266,000	5,091,000
Capitalized research and development	3,533,000	3,469,000
Deferred revenue	1,948,000	1,924,000
Other, net	1,020,000	249,000
Total deferred tax asset	54,669,000	40,040,000
Valuation allowance for deferred tax assets	(54,669,000)	(40,040,000)
	$ —	$ —

The increase in the valuation allowance of approximately $14.6 million is attributable to the increase in deferred tax assets, primarily due to the increase of net operating losses and tax credits.

A portion of the deferred tax assets related to net operating loss carryforwards as of December 31, 2003 include amounts related to stock option activity for which subsequent recognizable tax benefits, if any, will be credited to stockholders' equity.

8. Employee Benefit Plan

The Company has a 401(k) Savings Plan covering substantially all employees that have been employed for at least three months and meet certain age requirements. Employees may contribute up to 15% of their compensation per year (subject to a maximum limit by federal tax law). The Company does not provide matching contributions to the 401(k) Savings Plan.

9. Visionex Agreements and Acquisition

Visionex was established in 1997, under the laws of Singapore, to engage in clinical, regulatory and marketing activities. During 1997, Visionex obtained from us the exclusive rights to register, import, market, sell and distribute Vitrase® and a product called Keraform® in East Asian markets, excluding Japan and Korea, for which Visionex paid us $5.0 million. Prior to our acquisition of Visionex (discussed below), investors who owned 66% of ISTA shares controlled 100% of Visionex shares.

On March 8, 2000, we acquired Visionex by entering into an agreement with Visionex shareholders whereby we issued 3,319,363 shares of our Series C preferred stock, convertible into 245,879 shares of our common stock, to acquire all of the outstanding capital stock of Visionex. We assigned a fair value of $11.70 per share to the 3,319,363 shares of Series C preferred stock issued to effect the acquisition, at which time we recorded a deemed dividend of $19.2 million to recognize the excess of the value of the shares issued over the net assets acquired.

Under Singapore tax law, Visionex was subject to a 15% withholding tax on a $5.0 million license that it paid to us in connection with a license to market, sell and distribute Vitrase® and our other corneaplasty products in certain countries in Southeast Asia. This withholding tax was waived by the Economic Development Board, or EDB, of Singapore subject to various conditions, including a commitment that Visionex would implement a proposed project to expand its business activities in Singapore to the benefit of the local economy. We substantially wound down Visionex operations in July 2002, and the proposed project was never implemented. Based upon a letter we recently received from the EDB and our assessment of our obligations with the EDB, management does not believe that we will be required to pay any withholding tax or related obligations in connection with the license fee. However, if we are required to pay this withholding tax, we do not believe such payment would have a material adverse effect on the Company's business.

The Company's consolidated financial statements for 2003 and 2002 include the operations of Visionex since the date of acquisition.

10. Allergan Agreement

In March 2000, the Company entered into a license agreement with Allergan, under which Allergan will be responsible for the marketing, sale and distribution of Vitrase® for the back of the eye, in the United States and all international markets, except Mexico (until April 2004) and Japan. Under a related supply agreement, the Company will supply all of Allergan's requirements of Vitrase® at a fixed price per unit subject to certain future adjustments. The term of the license is ten full years after the date of the first commercial sale. Profits on the sale of Vitrase® for the back of the eye, in the United States will be shared equally between Allergan and the Company. The Company is responsible for all costs of product development, preclinical studies and clinical trials of Vitrase® and may receive up to $35.0 million in payments from Allergan upon the achievement of specified regulatory and development objectives.

The Company also issued 1,776,199 shares of Series D preferred stock to Allergan at $5.63 per share for proceeds of approximately $10.0 million. These shares were converted into 102,407 shares of common stock upon completion of the Company's initial public offering.

11. Otsuka Agreement

In December 2001, the Company entered into a license agreement with Otsuka Pharmaceuticals, Co. Ltd., under which Otsuka will be responsible for the marketing, sale and distribution of Vitrase® in Japan. Under a related supply agreement, the Company will supply all of Otsuka's requirements of Vitrase® at a fixed price per unit subject to certain future adjustments.

The term of the license is the later of fifteen years from the date of first commercial sale of Vitrase® in Japan or the expiration of the last valid claim of the licensed patents. Currently, no patents for Vitrase® have been issued in Japan.

The Company is responsible for all costs related to manufacturing, while Otsuka is responsible for preclinical studies, clinical trials and regulatory approval of Vitrase® in Japan. In December 2001, the Company received an initial license payment of $5.0 million and may receive an additional license payment upon regulatory approval of Vitrase® in Japan. Due to the Company's continuing involvement with Otsuka under the license agreement and related supply agreement, the $5.0 million license fee was recorded as deferred revenue as of December 31, 2001 and is being amortized over the estimated life of the license agreement of 18 years.

12. AcSentient Agreement

In May 2002, the Company acquired substantially all the assets of AcSentient, Inc. The assets include United States marketing rights for a new formulation of timolol, which the Company has named Istalol™, a beta-blocking agent for treating glaucoma. AcSentient previously acquired rights to this compound from Senju. The assets acquired from AcSentient also included United States product rights to Xibrom™, a topical non-steroidal anti-inflammatory compound for the treatment ocular inflammation, and worldwide marketing rights for Caprogel®, a novel compound for the treatment of hyphema. AcSentient previously acquired the rights to these two compounds from Senju and the Eastern Virginia Medical School, respectively.

The Company acquired the rights to these three compounds in exchange for $290,000 and 10,000 shares of the Company's common stock valued at $99,000 ($9.90 per share). Additionally, the Company assumed the liabilities of two milestone payments to Senju ($750,000 and $500,000), a milestone payment to the Eastern Virginia Medical School ($65,000), legal expenses associated with the acquisition ($20,000) and a patent application fee for Caprogel® ($4,500). As of the date these compounds were acquired, they had not achieved feasibility and there is no significant alternative future use should the Company's development efforts prove unsuccessful. Accordingly, the Company recorded an acquired in-process research and development charge of $1,728,500 in May 2002 related to the purchase of these compounds.

The NDA for Istalol™ was submitted by Senju to the FDA in September 2002. The NDA included data from pre-clinical studies conducted in Japan, combined with data from a Phase I clinical study conducted in the United States and a multi-center Phase III clinical study recently completed in the United States. We completed our Phase III studies of Xibrom™ and announced initial results of our clinical studies in March 2004. Based on the initial results of our Phase III studies, we anticipate submitting a NDA for Xibrom™ in the second quarter of 2004. The Company is currently conducting feasibility studies for the commercialization of Caprogel®. Once completed, and if these studies yield promising results, the Company intends to pursue further clinical development of Caprogel® consistent with such studies' results. However, the timing and scope for our development of Caprogel® may change based on our assessment, from time to time, of this product candidate's market potential, other product opportunities and our corporate priorities.

The Company also issued 84,567 shares of common stock to Otsuka Pharmaceuticals, Co. Ltd. at $47.30 per share in a private placement for net proceeds of approximately $4.0 million.

13. Geographic Information

During 2003, the Company purchased certain laboratory and production equipment for use in the UK. In years past, the Company also purchased certain laboratory and production equipment in Mexico. Laboratory and production equipment located in these countries totaled $653,000, $632,000 and $443,000 at December 31, 2003, 2002 and 2001, respectively.

The Company also has certain obligations denoted in foreign currency relating to clinical trials in Mexico, the UK, Poland, Germany, and the Netherlands. At December 31, 2003, 2002 and 2001 these obligations totaled $0, $33,000 and $61,000, respectively.

14. Shareholder Rights Plan

During January 2002, the Company adopted a Shareholder Rights Plan, whereby the Company issued a dividend of one right for each share of common stock of the Company held by stockholders of record as of the close of business on January 25, 2002. The plan was designed to contribute to the preservation of the Company's long-term value for its stockholders and assure the stockholders' fair value in the event of a future unsolicited business combination or similar transaction involving the Company.

EXHIBIT INDEX

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of registrant (1)
3.2	Certificate of Correction to Restated Certificate of Incorporation (1)
3.3	Certificate of Correction to Restated Certificate of Incorporation (2)
3.3	Bylaws of the registrant, as amended (1), (3)
3.4	Certificate of Amendment to Bylaws of the registrant
4.1	Specimen common stock certificate (3)
4.2	Preferred Stock Rights Agreement, dated as of December 31, 2001, between the registrant and Mellon Investor Services LLC (4)
4.3	First Amendment to the Preferred Stock Rights Agreement with Mellon Investor Services LLC, dated November 18, 2002 (5)
10.1	Amended and Restated Investors Rights Agreement dated as of March 29, 2000 (3)
10.2	1993 Stock Plan and forms of agreements thereunder (3)
10.3	2000 Stock Plan, as amended and restated, and forms of agreements thereunder (3), (18)
10.4	2000 Employee Stock Purchase Plan, as amended (3)
10.5	Form of Indemnification Agreement with executive officers and directors (3)
10.6	Clinical Development Agreement between Covance, Inc. and the registrant dated as of October 28, 1998, as amended (3)
10.7	Agreement between CroMedica Global Inc. and the registrant as of September 8, 1998 (3)
10.8	Agreement between CroMedica Global Inc. and the registrant as of May 19, 1999 (3)
10.9	Lease between the registrant and Aetna Life Insurance Company dated September 13, 1996 for leased premises located at Suite 100, 15279 Alton Parkway, Irvine, California (3)
10.10	Distributor Agreement between Laboratorios Sophia S.A. de C.V. and the registrant as of April 23, 1998 (3)
10.11	Supply Agreement between Biozyme Laboratories, Ltd. and the registrant as of September 23, 1999 (3)
10.12	License Agreement between Allergan Sales, Inc., Allergan Sales, Ltd. and the registrant as of March 29, 2000 (3), (6)
10.13	Supply Agreement between Allergan Sales, Inc., Allergan Sales, Ltd. and the registrant as of March 29, 2000 (3), (6)
10.14	Amendment No. 1 to Contract Clinical Research Agreement with CroMedica Global, Inc., dated May 19, 1999 (7)
10.15	Amendment No. 2 to Contract Clinical Research Agreement with CroMedica Global, Inc., dated May 19, 1999 (7)
10.16	License Agreement between Otsuka Pharmaceutical Co., Ltd., and the registrant, dated as of December 13, 2001 (6), (8)

Exhibit Number	Description
10.17	Supply Agreement between Otsuka Pharmaceutical Co., Ltd., and the registrant, dated as of December 13, 2001 (6), (8)
10.18	Securities Purchase Agreement between Otsuka Pharmaceutical Co., Ltd., and the registrant, dated as of December 13, 2001 (6), (8)
10.19	Registration Rights Agreement between Otsuka Pharmaceutical Co., Ltd., and the registrant, dated as of December 13, 2001 (6), (8)
10.20	Amendment No. 3 to Contract Clinical Research Agreement with CroMedica Global, Inc., dated December 5, 2001 (9)
10.21	Executive Employment Agreement between Vicente Anido, Jr., Ph.D. and the registrant, dated December 21, 2001 (9)
10.22	Stand-Alone Stock Option Agreement between Vicente Anido, Jr., Ph.D. and the registrant, dated December 21, 2001 (9)
10.23	Facility Lease Amendment No. 1 with Alton Plaza Property, Inc. (9)
10.24	Facility Lease Amendment No. 2 with Alton Plaza Property, Inc. (9)
10.25	Asset Purchase and Sale Agreement with AcSentient, Inc., dated May 3, 2002 (10)
10.26	Master Services Agreement with R.P. Scherer West, Inc. doing business as SP Pharmaceuticals, dated June 7, 2002 (11)
10.27	Form of Change in Control Severance Agreement with certain officers (12)
10.28	Form of Change in Control Severance Agreement with Thomas A. Mitro and Kirk McMullin (12)
10.29	Note and Warrant Purchase Agreement between the registrant and Investors, dated September 19, 2002 (16)
10.30	Form of Warrant issued under the Note and Warrant Purchase Agreement (13)
10.31	Common Stock and Warrant Purchase Agreement between the registrant and Investors, dated September 19, 2002 (16)
10.32	Form of Warrant to be issued under the Common Stock and Warrant Purchase Agreement (13)
10.33	Individual Non-Qualified Stock Option Agreement between Thomas A. Mitro and the registrant, dated July 1, 2002 (14)
10.34	Individual Non-Qualified Stock Option Agreement between Kirk McMullin and the registrant, dated August 5, 2002 (14)
10.35	Bausch & Lomb Pharmaceuticals, Inc. Contract Manufacturing Supply Agreement with registrant, dated November 25, 2002 (17)
10.36	Bausch & Lomb Pharmaceuticals, Inc. Contract Manufacturing Supply Agreement with registrant, dated February 6, 2003 (17)
10.37	License Agreement between the Eastern Virginia Medical School, and AcSentient, Inc., dated as of January 29, 2002 (17)

Exhibit Number	Description
10.38	Addendum between the Eastern Virginia Medical School, and AcSentient, Inc., dated as of April 30, 2002 (6), (15)
10.39	Letter regarding consent to assignment of License Agreement from AcSentient, Inc. to the Eastern Virginia Medical School, dated April 26, 2002 (15)
10.40	License Agreement between Senju Pharmaceutical Co., Ltd. and AcSentient, Inc., dated March 7, 2002 (17)
10.41	Agreement between Senju Pharmaceutical Co., Ltd. and AcSentient, Inc., dated April 17, 2002 (17)
10.42	Series D Preferred Stock Purchase Agreement between Allergan Pharmaceuticals (Ireland) Ltd., Inc., and registrant, dated as of March 29, 2000 (3)
10.43	Amendment to Xibrom™ License Agreement between Senju Pharmaceutical Co., Ltd., and registrant, dated August 13, 2002 (6), (15)
10.44	Amendment to Timolol Agreement between Senju Pharmaceutical Co., Ltd., and registrant, dated August 13, 2002 (6), (15)
10.45	Amendment No. 4 to Contract Clinical Research Agreement with CroMedica Global, Inc., dated August 18, 2003.
21.1	Subsidiaries of the registrant (3)
23.1	Consent of Ernst & Young LLP
24.1	Power of Attorney (included in the signature page to this registration statement on page II-5)
31.1	Certification of the Chief Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of the Chief Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification of the Chief Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification of the Chief Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002.

(1) Incorporated by reference to the registrant's report on Form 10-K for the year ended December 31, 2002, filed with the Commission on March 7, 2003.

(2) Incorporated by reference from the registrant's report on Form 8-K filed with the Commission on April 9, 2003.

(3) Incorporated by reference to the registrant's Registration Statement on Form S-1 (File No. 333-34120).

(4) Incorporated by reference to the registrant's report on Form 8-A filed with the Commission on January 22, 2002.

(5) Incorporated by reference from the registrant's Registration Statement on Form 8-A12G/A filed with the Commission on November 19, 2002.

(6) Confidential treatment requested as to certain portions.

(7) Incorporated by reference to the registrant's report on Form 10-K for the year ended December 31, 2000, filed with the Commission on March 30, 2001.

(8) Incorporated by reference from the registrant's report on Form 8-K filed with the Commission on January 2, 2002.

(9) Incorporated by reference from the registrant's report on Form 10-K for the year ended December 31, 2001, filed with the Commission on April 1, 2002.

(10) Incorporated by reference from the registrant's report on Form 8-K filed with the Commission on May 6, 2002.

(11) Incorporated by reference from the registrant's report on Form 8-K filed with the Commission on July 9, 2002.

(12) Incorporated by reference from the registrant's report on Form 10-Q for the period ended June 30, 2002 filed with the Commission on August 14, 2002.

(13) Incorporated by reference from the registrant's report on Form 8-K filed with the Commission September 25, 2002.

(14) Incorporated by reference from the registrant's Registration Statement on Form S-8 filed with the Commission on February 18, 2003.

(15) Incorporated by reference from the registrant's report on Form 10-K/A for the period ended December 31, 2002 filed with the Commission on April 30, 2003.

(16) Incorporated by reference from the registrant's report on Form 10-K/A for the period ended December 31, 2002 filed with the Commission on May 14, 2003.

(17) Incorporated by reference from the registrant's report on Form 10-K/A for the period ended December 31, 2002 filed with the Commission on June 4, 2003.

(18) Incorporated by reference from the registrant's report on Form 10-Q for the period ended June 30, 2003 filed with the Commission on August 14, 2003.