SCIOS INC
Form 10-K/A
May 29, 2001

==========

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K/A
(Amendment No. 1)

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

For the fiscal year ended December 31, 2000

OR

[_] TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission File Number 0-11749

SCIOS INC.

(Exact name of registrant as specified in its charter)

DELAWARE	95-3701481
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

820 West Maude Avenue, Sunnyvale, California 94086
(Address of principal executive offices)

Registrant's telephone number, including area code: (408) 616-8200

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

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

Common Stock, $0.001 par value
Contingent Payment Rights

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 X 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.

The approximate aggregate market value of voting stock held by nonaffiliates of the registrant as of March 16, 2001 was $737,569,844.

As of March 16, 2001, 39,314,425 shares of the registrant's Common Stock were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Documents	Form 10-K Part
Definitive Proxy Statement with respect to the 2001 Annual Meeting of Stockholders	III

==========

EXPLANATORY NOTE

By filing this amendment to our Annual Report on Form 10-K for the year ended December 31, 2000, Scios Inc. is amending the first bulletpoint of Part 1, "Item 1. Business--Natrecor--Natrecor Clinical Trials--The VMAC Trial" of its Annual Report on Form 10-K for the year ended December 31, 2000 to include the percentage decreases in pulmonary capillary wedge pressure, or PCWP, for patients treated with Natrecor and for the patients treated in the placebo group after three hours of treatment in our VMAC clinical trial. This information was inadvertently omitted from our Form 10-K filed with the Securities and Exchange Commission on March 30, 2001. Other than the above-referenced change, the information set forth below is identical to the information set forth under "Item 1. Business" in our Annual Report on Form 10-K filed with the SEC on March 30, 2001.

PART I

In this Form 10-K, "Scios", "we"," us", and "our" refer to Scios Inc. The following discussion contains forward-looking statements about our plans, objectives and future results. These forward-looking statements are based on our current expectations. We assume no obligation to update this information. Realization of our plans and hoped for results involves risks and uncertainties, and our actual results could differ materially from those discussed here. Factors that could cause or contribute to such differences include, but are not limited to, those discussed below in this Form 10-K for the year ended December 31, 2000, particularly in the section entitled "Risk Factors".

Item 1. BUSINESS

Overview

We are a biopharmaceutical company developing novel treatments for cardiovascular and inflammatory diseases. We are distinguished by our disease-based technology platform, which integrates expertise in protein biology with computational and medicinal chemistry to identify novel targets and protein-

based small molecule compounds for large markets with insufficient treatments. Our lead product candidates include, Natrecor (nesiritide), for the treatment of acute congestive heart failure, or acute CHF, for which we have filed a New Drug Application, or NDA, with the FDA, and our p38 kinase inhibitor, SCIO-469, for the treatment of inflammatory diseases such as rheumatoid arthritis, which is currently in Phase Ib clinical trials.

We were incorporated in California in 1981 under the name California Biotechnology Inc. and reincorporated in Delaware in 1988. We changed our name to Scios Inc. in February 1992, and to Scios Nova Inc. in September 1992 following our acquisition of Nova Pharmaceuticals, Inc. We returned to using the name Scios Inc. in March 1996. Since September 1999, our principal executive offices have been located at 820 West Maude Avenue, Sunnyvale, California 94085. Our telephone number is (408) 616-8200.

Our corporate website is located at www.sciosinc.com. We do not intend for information found on our website to be part of this document.

We own various copyrights, trademarks and trade names used in our business including the following: Natrecor(R), Gliadel(R) and Fiblast(R). This document also includes trademarks, service marks and trade names of other companies, including the following: Biodel(R), Enbrel(R), Remicade(R), Celebrex(R), Vioxx(R), Tezosentan(R), Risperdal(R), Simdax(R), Paxil(R), Eskalith(R), Eskalith CR(R), Stelazine(R), Thorazine(R) and Parnate(R).

Recent Developments

Since December 31, 2000, the following significant developments have occurred with respect to our business:

Natrecor- for the treatment of acute CHF

- In January 2001, we filed an amendment to our NDA for Natrecor with the FDA. We believe the FDA will respond to our application by July 2001.

- In January 2001, we entered into a marketing alliance with Innovex L.P. to commercialize Natrecor for the treatment of acute CHF. Innovex will deliver a wide range of sales and marketing solutions for us, including hiring, training and deploying a dedicated cardiology and emergency medicine sales force of approximately 180 salespeople.

p38 Kinase Inhibitor Program- SCIO-469 for the treatment of inflammatory diseases

- In January 2001, we completed a Phase Ia trial of SCIO-469. The trial indicated that the drug is safe and well-tolerated when given as a single dose to healthy volunteers.

- In February 2001, we began a Phase Ib trial to evaluate the safety, tolerability and pharmacokinetics of multiple oral doses of SCIO-469. The results of this trial are expected in the second quarter of 2001.

Other Developments

In March 2001, we and GlaxoSmithKline Corporation, or GSK, agreed to terminate the exclusive marketing agreement relating to certain GSK psychiatric products sold by us effective March 31, 2001. Under the agreement, the Company will receive from GSK $4.0 million in 2001, $3.0 million in 2002 and $2.5

million in 2003. Approximately 40% of our total revenues in 2000 were derived from these psychiatric products.

Our Lead Products in Development

We currently have two lead products in clinical development: Natrecor for the treatment of acute CHF, and SCIO-469, a novel small molecule compound for the treatment of inflammatory diseases.

Natrecor

Congestive Heart Failure

According to the 2001 American Medical Association Heart and Stroke Statistical Update, five million Americans currently suffer from chronic CHF and 550,000 new cases of CHF will be diagnosed in the United States this year. Annual expenditures for CHF are estimated to be $38 billion, including $23 billion for inpatient care. CHF represents the largest single expenditure of the Medicare system.

Chronic CHF is characterized by a progressive loss in the heart's ability to pump blood. It is attributable to weakening of the contractile cells of the heart and accumulation of scar tissue. Different diseases can cause CHF, including coronary artery disease, heart attacks, inflammation of the heart tissue and diseases of the heart valves. Weakened heart muscle often results in poor cardiac output because the heart is unable to empty blood adequately from the ventricles to the circulation with each beat. Blood begins to back up and pool in the ventricles, and the heart changes from its normal shape and becomes enlarged. Subsequently, blood begins to back up into the blood vessels of the lungs, causing marked increases in pulmonary vascular pressures. As pressure increases, fluid moves from the pulmonary blood vessels into the air spaces, causing pulmonary congestion. One frequently used measurement of pulmonary vascular pressure is pulmonary capillary wedge pressure, or PCWP.

CHF symptoms that result from the pooling of blood include dyspnea, or shortness of breath, edema, or fluid

retention, and swelling of the legs and feet. CHF symptoms that result from the inefficiency of the heart to distribute or adequately pump oxygen-rich blood to body tissues include fatigue and weakness as well as a loss of appetite. As the disease progresses, these symptoms can severely impact the patient's quality of life, such that even the ability to perform simple tasks, such as walking across the room, becomes limited.

In the early stages of CHF, the body activates several hormonal pathways that help the heart compensate in the short-term but have adverse long-term effects. These hormones, which include adrenalin, angiotensin II, aldosterone and endothelin, stimulate the heart to beat faster and stronger, thicken the wall of the heart and maintain blood pressure by constricting blood vessels and stimulating the kidney to retain sodium. If these pathways remain activated over a sustained period of time, the beneficial effects are lost and injurious effects develop, contributing to an eventual deterioration of heart function. Current medications and medications under development generally focus on one or more of these hormonal pathways.

Many CHF patients experience a rapid deterioration, or decompensation, of their disease and require urgent treatment in the hospital. This is called acute CHF. Acute CHF accounts for approximately one million hospital admissions each year in the United States. Acute CHF is the most frequent cause of

hospitalization in patients older than 65 years. In addition, patients suffering from acute CHF have a five-year mortality rate of approximately 50%. For more than a decade, there have been no new FDA-approved drugs to treat acute CHF.

Current Treatments for Congestive Heart Failure

While some cardiac risk factors such as smoking, high cholesterol, high blood pressure, diabetes and obesity can be controlled with lifestyle changes, the majority of patients with CHF require additional treatments to help manage their disease. Current medications for the treatment of CHF, including diuretics, inotropes, vasodilators and beta blockers, only focus on single components of the diverse pathways contributing to CHF. Diuretics help the kidneys rid the body of excess fluid, thereby reducing blood volume and the heart's workload. Inotropes strengthen the heart's pumping action. Vasodilators, such as ACE inhibitors, cause the peripheral arteries to dilate, making it easier for blood to flow. Beta blockers slow the heart rate and reduce blood pressure by blocking the effects of adrenalin.

Upon arrival at the emergency room, patients who experience acute episodes of CHF are typically treated with a combination of oxygen, morphine and intravenous diuretics. A small percentage of patients respond to this initial therapy and do not require admission to the hospital; however, the majority of acute CHF patients require additional medical intervention and are admitted. Additional acute CHF treatments may include intravenous administration of inotropes, such as dobutamine, and vasodilators, such as nitroglycerin. While each of these therapies assist in managing acute CHF, each also has inherent limitations. Inotropes strengthen the contractility of the heart but increase the incidence of cardiac arrhythmias, or irregular heartbeats, and are associated with increased mortality. Intravenously administered nitroglycerin requires careful monitoring and slow dosage increases in small increments, resulting in delays in attaining positive responses in acutely ill patients. Moreover, therapeutically effective doses of IV nitroglycerin are:

- unpredictable from patient to patient;
- very close to the toxic side effects of hypotension; and
- associated with increased tolerance or loss of effectiveness.

These complications of IV nitroglycerin often require the transfer of acute CHF patients to more costly treatment units within the hospital, such as the cardiac and intensive care units, in order to provide careful patient monitoring.

Natrecor: Our Solution for the Treatment of Acute Congestive Heart Failure

Natrecor is a recombinant form of human b-type natriuretic peptide, or BNP, a naturally occurring hormone in

the body that aids in the healthy functioning of the heart. BNP is secreted by the ventricles of the heart as a response to CHF. The advantage of Natrecor, compared to existing forms of therapy for acute CHF, is that it works on multiple components of the acute CHF disease pathway. In particular, Natrecor:

- dilates veins and arteries, decreasing the resistance against which the heart has to pump;
- stimulates the kidney to excrete excess fluid; and
- has been shown to oppose many of the long-term injurious factors

presented by hormones such as adrenalin, angiotension II, aldosterone and endothelin.

In clinical trials, Natrecor has also been shown to significantly improve blood circulation and patient symptoms compared to IV nitroglycerin without the need for labor-intensive monitoring, and its method of administration does not require frequent dosing adjustments. In addition, Natrecor is not associated with any increase in the incidence of cardiac arrhythmia and demonstrates no evidence of drug interactions with other agents used concurrently in the treatment of acute CHF.

Natrecor Clinical Trials

We have conducted numerous clinical trials evaluating Natrecor over the past eight years. Approximately 1,000 patients have been treated with Natrecor in 12 trials, including four pivotal efficacy trials. In all of these trials, Natrecor administration has been associated with improved blood circulation and vascular filling pressures in the heart and lungs. Each of the efficacy trials further demonstrated statistically significant improvement of symptoms in acute CHF patients.

Amended NDA Submission Trials

We have completed two trials since the submission of our original NDA, the VMAC trial, or Vasodilation in the Management of Acute CHF, and the PRECEDENT trial, or Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy, and form the basis of our amended NDA.

The VMAC Trial. We began enrollment in our VMAC study in July 2000 and in October 2000, completed enrollment of 498 patients hospitalized for acute CHF in the United States. This trial compared the effects of Natrecor, IV nitroglycerin or placebo, when individually added to standard therapy, such as diuretics and inotropes. The primary endpoints were a reduction in pulmonary capillary wedge pressure, or PCWP - a measure of the pulmonary vascular pressure of the heart, reflecting its workload - and improvement of the symptom of shortness of breath. The VMAC trial achieved both of its primary endpoints. Key results of the VMAC trial that were presented in November 2000 at the annual scientific meeting of the American Heart Association include:

- Natrecor produced a 20% decrease in PCWP at three hours, most of which occurred in the first 15 minutes, which was significantly better than a 7% decrease in PCWP at three hours for the placebo group;

- Natrecor improved shortness of breath significantly better than placebo;

- Natrecor decreased PCWP significantly faster and to a greater extent than IV nitroglycerin;

- Natrecor significantly improved breathing in patients receiving standard active therapy; in contrast, IV nitroglycerin did not significantly improve breathing in these patients;

- Natrecor-treated patients had significantly fewer adverse events than either placebo or IV nitroglycerin patients;

- acute CHF patients experiencing active ischemia, which is impaired blood flow to the heart, showed no adverse side effects in response to Natrecor; and

- patients receiving Natrecor did not develop tolerance to the drug over time, consequently, unlike IV nitroglycerin, the effects of Natrecor were sustained through 24 hours at the same dosage.

The PRECEDENT Trial. The PRECEDENT trial compared Natrecor and dobutamine, the most commonly used inotrope treatment for acute CHF. Key results of the PRECEDENT trial indicated that:

- Natrecor produced fewer cardiac arrythmias than dobutamine; and

- use of Natrecor was associated with fewer deaths than the use of dobutamine.

Initial NDA Clinical Trials

We conducted three pivotal Phase III clinical trials that were submitted to the FDA in our original NDA for Natrecor.

Trial 704.311. Trial 704.311 was our first Phase III clinical trial that we conducted to evaluate the efficacy of Natrecor in patients with acute CHF. In this trial, we enrolled 103 patients who were treated with one of three intravenously administered doses of Natrecor over a 24-hour period. This trial demonstrated that Natrecor produced significant improvements in PCWP and cardiac pump function. Results of this study were published in The Journal of the American College of Cardiology in July 1999.

Trial 704.325. Trial 704.325, our second Phase III clinical trial, was a double-blind, placebo-controlled trial which consisted of 127 patients and was designed to determine the short-term efficacy of Natrecor with regard to hemodynamic measures and symptoms. In this trial, Natrecor demonstrated statistically significant improvements in multiple symptoms of acute CHF, such as severe shortness of breath and fatigue. In addition, patients treated with Natrecor also experienced improvements in blood circulation, vascular pressures in the heart and lungs and cardiac pumping ability. The results from this trial were published in the July 2000 issue of The New England Journal of Medicine.

Trial 704.326. In our third Phase III clinical trial, we enrolled 305 patients and demonstrated that Natrecor resulted in the rapid and statistically significant improvement of the symptoms and clinical severity of acute CHF, when compared to placebo. Patients not receiving Natrecor received one or more standard intravenous drugs for acute CHF, most commonly dobutamine, milrinone or nitroglycerin. The trial also compared Natrecor with standard intravenous agents with respect to adverse events. The safety of Natrecor was demonstrated to be equal to the safety of standard intravenous drugs for acute CHF. The trial also demonstrated patients treated with Natrecor experienced a reduced need for diuretics. The results from this trial were also published in the July 2000 issue of The New England Journal of Medicine.

In each of these trials, Natrecor demonstrated efficacy with respect to symptoms and hemodynamic parameters of acute CHF. The most common adverse event in the patients treated with Natrecor was dose-related hypotension, which was usually asymptomatic.

Current Clinical Trials

In March 2001, we began a new clinical trial aimed at investigating the potential pharmaco-economic impact of Natrecor in improving treatment and outcomes for acute CHF patients. This PROACTION trial, or Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor, is a pilot study designed to compare the clinical effects, safety profile and costs of standard therapy plus

Natrecor to standard therapy plus placebo in 250 acute CHF patients treated in the emergency room or an observation unit. We expect to complete this study during the third quarter of 2001.

NDA Filings

In April 1998, we submitted an NDA to the FDA for the use of Natrecor for the treatment of acute CHF. This NDA was based on the efficacy trials, 704.311, 704.325 and 704.326. In January 1999, the Cardiovascular and Renal Advisory Committee recommended that the FDA approve Natrecor for the treatment of acute CHF. In April 1999, we received a non-approval letter from the FDA, requesting that we conduct further studies with Natrecor. The FDA requested that in these studies we demonstrate:

- the clinical utility of Natrecor as compared to the current standard of care vasodilator therapy, IV nitroglycerin;
- that Natrecor is safe in acute CHF patients experiencing active ischemia; and
- that the clinical benefits of Natrecor occur early after the initiation of therapy.

The VMAC trial was designed to address each of the issues raised by the FDA in its non-approval letter. The data from the VMAC study and the PRECEDENT study were submitted to the FDA in our amendment to the NDA for Natrecor in January 2001. We expect the FDA to respond to our amended NDA by July 2001.

p38 Kinase Inhibitor Program

The Immune System and Inflammation

The immune system is composed of multiple cell types, including white blood cells, each with a specific functional role. This system is regulated by cytokines, which are proteins produced by immune system cells. When the body encounters foreign material, or when tissue injury occurs, numerous enzymes in the immune system are activated, causing the production of various inflammatory cytokines such as interleukin-1, or IL-1, and tumor necrosis factor, or TNF.

One class of the immune system's family of enzymes is the mitogen-activated protein kinases, or MAP kinases. The MAP kinases are a family of intracellular signaling enzymes that are activated when cells are either stimulated or stressed and mediate many beneficial and injurious cellular responses. One of the MAP kinases, p38 kinase, is responsible for increased production of IL-1, TNF and the inflammatory enzyme cyclooxygenase-2, or COX-2.

Autoimmune diseases occur when the immune system is abnormally activated against its own body. In the case of rheumatoid arthritis, the immune system is activated against joint tissues. White blood cells then invade the joint space, and, when activated, produce IL-1, TNF and COX-2, which result in pain, swelling and eventual destruction of the affected joints. Other diseases that are worsened by sustained high levels of TNF and IL-1 include inflammatory bowel disease, CHF and neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease.

Current Therapy for Autoimmune and Inflammatory Diseases

Currently, there is no cure or prevention for autoimmune disease. Optimal medical management requires the early introduction of therapies in order to

prevent the long-term effects of the disease. In the case of rheumatoid arthritis, long-term effects include irreversible joint damage and hypertrophy of joint tissues limiting a patient's ability to move the affected joints.

Traditionally, initial drug treatment of inflammatory diseases involves the use of non-steroidal anti-inflammatory agents. Steroids, such as glucocorticoids, are often added as the disease or symptoms progress. Although these agents help patients increase function and improve symptoms, they do not stop progression of the disease. Moreover, these drugs have been demonstrated to cause both stomach and kidney problems. In addition,

persistent steroid treatment may result in excess suppression of the immune system, which can lead to infection, decreased bone marrow function and osteoporosis. Recently, more selective anti-inflammatory agents, or COX-2 inhibitors, such as Celebrex and Vioxx, have been introduced for symptom relief; however, they do not alter the progression of inflammatory disease. Sales of COX-2 inhibitors for the treatment of inflammatory disease were approximately $4.8 billion in 2000.

More powerful drugs exist for patients that do not respond to initial drug therapy. In the case of rheumatoid arthritis, drugs such as methotrexate, hydroxychloroquine and sulfasalazine can have individual side effects which must be monitored closely, and a delay of one to six months for a clinical response is common.

Within the past four years, inhibition of inflammatory cytokines has become an established treatment for autoimmune disease. In the case of rheumatoid arthritis, two new protein therapeutics, Enbrel and Remicade, were introduced to inhibit the effects of TNF. These treatments have been shown to be effective at reducing disease activity; however, they must be given by injection or infusion on a repeated basis, which is cumbersome for chronic diseases. In addition, when taken on a chronic basis, increased rates of infections have been reported in patients taking these medications because these new therapies result in an excessive inhibition of TNF upon injection due to the limited ability to adjust the dose of drug administered. Resistance to the treatment is also an issue with these new drugs. This is due in part to increasing production by a patient's immune system of antibodies that neutralize administered proteins.

We are focusing our initial drug development efforts on creating an orally available small molecule drug for the treatment of rheumatoid arthritis. The Arthritis Foundation estimated that approximately 2.1 million Americans currently suffer from rheumatoid arthritis. Decision Resources, an independent market research group, suggests that the global market for rheumatoid arthritis therapies will be approximately $6.6 billion by 2009, up from almost $1.5 billion in 1999. Rheumatoid arthritis patients generate more than nine million physician office visits and more than 250,000 hospitalizations each year. It is estimated that, in aggregate, the average yearly earnings deficits for all working individuals with rheumatoid arthritis is approximately $6.5 billion.

SCIO-469: Our p38 Kinase Inhibitor for the Treatment of Inflammatory Diseases

A small molecule inhibitor of p38 kinase may have advantages in the treatment of inflammatory disease since it could inhibit the production of TNF, IL-1 and COX-2. Our lead p38 kinase inhibitor is SCIO-469. We believe that patients treated with a p38 kinase inhibitor could experience a reduction in both the symptoms of rheumatoid arthritis and the progression of the disease. We also believe another key potential advantage of our approach resides in the ability of our oral product to be prescribed in a manner that allows for careful dosage adjustment. Dosage adjustment may allow the physician to inhibit TNF

sufficiently to obtain a useful therapeutic effect without subjecting the patient to the risk of infection associated with complete TNF inhibition.

In preclinical studies of acute and chronic inflammatory arthritis, orally administered doses of SCIO-469 reduced cellular production of COX-2 in a dose-dependent manner and reduced COX-2 and TNF levels in whole blood assays. Statistically significant reductions in inflammation also were observed in animal models of arthritis. In October 2000, we presented preclinical data involving our p38 kinase inhibitors at the annual scientific meeting of the American College of Rheumatology. The study demonstrated that our p38 kinase inhibitors had statistically significant anti-inflammatory effects in both acute and chronic animal models of inflammation.

In January 2001, we completed a Phase Ia trial of SCIO-469 in which single oral doses were shown to be safe and well tolerated. This Phase Ia trial enrolled 30 volunteers. In February 2001, we initiated a Phase Ib clinical trial with SCIO-469. This Phase Ib trial is a double-blind, placebo-controlled, multiple oral dose study to evaluate the safety and tolerability of multiple doses of SCIO-469. This trial is designed to enroll 20 healthy volunteers. If the results of our Phase Ib clinical trial are favorable, we plan to initiate a Phase II trial in rheumatoid arthritis patients in the fourth quarter of 2001. This will consist of testing the drug in patients with active disease, evaluating for both safety and efficacy over a range of doses.

Marketing and Sales

Natrecor

Pre-launch Objectives

In anticipation of possible FDA approval in July 2001, we are working to position Natrecor for maximum market penetration in the United States at the time of launch. We are developing awareness for Natrecor among key target audiences through a variety of tactical programs, including medical seminars, continuing medical education programs, advisory boards and publications. We have identified and are developing relationships with physicians and nurses who play a leading role in the diagnosis and treatment of CHF. We intend for these individuals to communicate the benefits of Natrecor through a series of medical symposia and lecture programs.

Our Agreement with Innovex

In January 2001, we entered into a marketing alliance with Innovex, which will deliver a wide range of sales and marketing solutions for us. We will lead strategic and tactical planning for the sales and marketing of Natrecor, and we will also maintain control over the clinical development for additional indications for Natrecor. Innovex will identify, hire, train and deploy a dedicated cardiology and emergency medicine sales force of approximately 180 people to launch Natrecor. Together with Innovex, we have established hiring, training and deployment criteria for the sales force. Commencing three years after Innovex begins to supply us with dedicated salespeople, we have the option to acquire all or any portion of this sales force from Innovex for a fee upon 90 days notice.

We will create a field support team of approximately 32 people. Twelve scientific affairs managers have already been hired and trained and are currently working in the field to build relationships with opinion-leading cardiologists. We have hired two area business directors and have begun the recruitment efforts to hire and train 18 area business managers to support the

Natrecor sales force.

PharmaBio, an affiliate of Innovex, has agreed to fund $30.0 million of our costs to launch Natrecor over the first 24 months of Natrecor's commercialization and to loan us up to $5.0 million. Of the $30.0 million, we anticipate that $10.0 million will paid to us in 2001 following FDA approval of Natrecor. We will receive 100% of the revenues from sales of Natrecor. In turn, we will pay PharmaBio a declining royalty rate on those revenues for the period from 2003 to 2007. We also granted PharmaBio a warrant to purchase 700,000 shares of our common stock at an exercise price of $20.00 per share.

Licensing Arrangements with Third Parties

We have licensed some of our product candidates to third parties, who are now responsible for product development. Under these arrangements, we typically receive a combination of upfront payments, milestone payments upon their achievement of scientific and clinical benchmarks and royalties on commercial sales of products by our partners.

BNP Diagnostics. We have licensed to Biosite Diagnostics, Inc. and Abbott Laboratories the right to use our patents on BNP for diagnostic purposes. Biosite has developed and is currently marketing a point-of-care diagnostic test for BNP levels in the United States and Europe. This test is used to identify individuals with CHF or to monitor progression of their disease or their response to treatment. We are currently receiving royalties from Biosite on the sales of their diagnostic products. Abbott is continuing to develop its BNP diagnostic product.

In 1998, we entered into a cross-license agreement with Shionogi and Co., Ltd. under which we granted Shionogi a royalty-free, nonexclusive license to our BNP patent rights for the diagnostic field. In exchange, Shionogi granted us a royalty-bearing, exclusive license under Shionogi's BNP patents to develop therapeutic products. For

therapeutic products, we pay royalties on net sales for the life of the patent in countries where Shionogi holds one or more BNP patents. In countries where Shionogi has BNP patents pending, we are obligated to pay a reduced royalty on the net sales of our therapeutic products until the earlier of the invalidity of the BNP patents pending or four years from the commencement of sales in that country of such therapeutic products.

Fibroblast Growth Factor. FGF, a naturally-occurring protein, stimulates the growth of new blood vessels. In November 1999, we granted a license to Chiron Corporation covering rights to FGF in the areas not previously licensed by us. We may receive up to $12.0 million in milestone payments upon Chiron's completion of certain development objectives. In addition, we will receive royalties based on sales of FGF products in countries where we hold patents. Chiron has completed separate Phase II human clinical trials evaluating FGF as treatment for coronary artery and peripheral vascular disease. In 1988, we licensed our FGF technology to Kaken Pharmaceutical Co., Ltd. Kaken has an approval pending in Japan to market an FGF-based product for the treatment of recalcitrant dermal wounds. We will receive royalties on any sales of FGF products by Kaken in Asia. We have also granted nonexclusive licenses under our FGF patents and technology to Orquest, Inc., for the development of products for the treatment of bone fractures.

We are obligated to make payments to Organon International based on amounts received by us upon commercialization of FGF. Approximately $218,000 remains to be paid under this obligation, which stems from our 1989 reacquisition of

certain FGF rights previously licensed to Organon.

Vascular Endothelial Growth Factor\\121\\. VEGF\\121\\ is a naturally-occurring protein used to stimulate the growth of new blood vessels. In May 1996, we granted a license to GenVec, Inc. for the use of the gene encoding VEGF\\121\\ in gene therapy products. GenVec is currently conducting clinical trials of its BIOBYPASS angiogen which incorporates the use of our licensed technology. This product is being evaluated to treat coronary artery disease and peripheral vascular disease. We will receive royalties on any future sales of these products.

Glucagon-like Peptide-1. GLP-1 is a potent peptide that stimulates insulin release when blood sugar levels are above normal. In 1988, we licensed from Massachusetts General Hospital the exclusive use of certain patent applications for GLP-1 and certain analogs upon which we will pay a royalty on any future sales. In 1996, we granted Novo Nordisk A/S an exclusive license to our GLP-1 technology and the additional rights we acquired pursuant to the Massachusetts General Hospital license. We will receive royalties on product sales made by Novo Nordisk A/S. Novo Nordisk A/S is responsible for development activities for GLP-1 and has initiated Phase II human clinical trials of a GLP-1 analog that they are developing as a treatment for Type 2 diabetes.

Alzheimer's Disease. We have separate research collaborations with Eli Lilly and Company and with DuPont Pharmaceuticals Corporation to develop new therapies for Alzheimer's Disease. The joint research phase of our collaboration with DuPont ended in November 2000. DuPont is continuing its efforts to develop a therapeutic for Alzheimer's disease based in part on our technology. The joint research phase of our collaboration with Eli Lilly is fully funded by Eli Lilly and has been extended through December 2001. We are entitled to receive potential milestone payments if certain events are achieved, and Eli Lilly is entitled to commercialize any resulting products subject to royalty payments to us.

Drug Delivery Systems. Prior to our acquisition of Nova Pharmaceutical Corporation in 1992, Nova had been developing several drug delivery systems, including the Gliadel implant to treat primary brain cancer. The Gliadel technology was developed pursuant to a license agreement with the Massachusetts Institute of Technology relating to MIT's Biodel drug delivery technology. We licensed Gliadel to Guilford Pharmaceuticals Inc. in 1994. Gliadel was approved for marketing in the United States in 1996. We assigned our Biodel license rights back to MIT, which will administer the licensing of this technology, including the license with Guilford. We and MIT are receiving royalty and milestone payments under the license agreement with Guilford. We conducted the Gliadel project on behalf of Nova Technology Limited Partnership, the limited partnership that funded Nova's research and development on these projects.

Psychiatric Sales and Marketing Division

Since 1990, our Psychiatric Sales and Marketing Division (PSMD) has had the exclusive right to market certain products in the United States under an agreement with GSK, including Eskalith and Eskalith CR, Thorazine, Stelazine, and Parnate. GSK was responsible for the manufacture and distribution of these products. As part of our agreement with GSK, we paid GSK 40% of our net profits from sales of these products.

From time to time, our PSMD has also marketed various psychiatric products on behalf of other companies under co-promotion agreements. We were compensated for our services based upon the number of sales calls we made. The last of these other agreements ended as of March 31, 2001.

In March 2001, we entered into an agreement with GSK under which GSK reacquired the right to market the GSK products. This agreement is effective as of March 31, 2001 and entitles us to receive payments from GSK of $4.0 million in 2001, $3.0 million in 2002 and $2.5 million in 2003. Given our decision to exit this line of business, we decided to terminate the employment of our part-time sales force and certain full-time support personnel in this division.

Research and Development

Our technical capabilities now include disease-based gene microarray, bioinformatics, structural informatics, and state-of-the-art medicinal chemistry, including computational chemistry modeling, all of which have added to our traditional technical strengths in protein cloning and expression.

In order to discover new pathways of disease, our research has assembled tissue samples from a broad array of human and experimental diseases of the cardiovascular system. We analyze these tissues for the expression of new genes that may be involved in particular diseases. We do this by a technique known as microarray gene display, in which fluorescent tags identify which genes may be up regulated or down regulated during the course of a particular disease. We then apply commercial and proprietary software analysis to the sequence of these genes and to the patterns of their expression in order to highlight cellular pathways that may be playing a particular role in a disease process. This process is known as bioinformatics.

Particular attention is paid either to the presence of a known enzyme participating unexpectedly in a disease process or to a novel enzyme. Our molecular biologists then express these candidate target enzymes in an activated state as pure proteins and develop high throughput screening assays to discover inhibitors of those enzymes within our chemical compound library, which we have developed over the last several years. Applying the tools of structural informatics, our protein chemists develop computer-based three-dimensional structures of these enzymes that guide our chemists in developing lead inhibitory molecules with respect to potency and selectivity. Once we have brought a drug candidate to the optimum level of potency and safety, we test the drug at both the cellular and animal level, again applying gene microarray technology. This allows the rapid evaluation of the drug for efficacy while ensuring that potential toxicities are minimized before testing in the clinic.

We are focused on diseases of the cardiovascular system, with a particular emphasis on inflammation in both its acute and chronic forms and scarring as a cause of chronic organ failure. Our research has emphasized an emerging family of protein therapeutic targets known as protein kinases. Kinases are naturally occurring intracellular signaling "switches" that work by attaching phosphate groups to other proteins, thereby activating cellular processes controlled by those proteins, including the transcription of new proteins. While the vast majority of protein kinases are engaged in beneficial work on behalf of the cells of the body, medical research over the last decade has clearly demonstrated that cellular pathways abnormally activated by certain kinases contribute to both the symptoms and progression of many diseases. By applying the most advanced technologies available with proprietary methodology, including the development of gene analysis software, we have dedicated ourselves to the identification of kinases participating in diseases within our strategic focus and developing and testing inhibitors of those enzymes for potential therapeutic value. The rapid preclinical and clinical development of our p38 kinase inhibitor, SCIO-469, represents the initial

success of this innovative approach.

Our aggregate research and development expense totaled $39.3 million in 2000, $34.3 million in 1999 and $46.6 million in 1998.

Manufacturing

Our products are manufactured for us by third parties. In 1995, we entered into an agreement with Biochemie GmbH in Austria for the manufacture of Natrecor. If Natrecor is approved by the FDA in 2001, we expect the agreement to run through 2009. Biochemie ships Natrecor in powder form to Abbott Laboratories in McPherson, Kansas, where it is blended, filled and packaged for shipment. We also maintain arrangements with several companies to manufacture our p38 kinase inhibitor compounds and intend to enter into a long-term supply relationship if our compounds continue to proceed through development.

Patents and Proprietary Rights

We seek patent protection for proprietary technology and products in the United States and abroad to prevent others from unfairly capitalizing on our investment in research. Other companies engaged in research and development of new health care products also are actively pursuing patents for their technologies. We also rely upon trade secrets and know-how to reinforce our competitive position. However, trade secret protection will not preclude others from independently developing technology similar to ours, nor can there be any assurance that third parties who have signed confidentiality agreements with us will honor those agreements.

We currently own or hold exclusive rights to approximately 69 issued U.S. patents and approximately 58 U. S. pending patent applications covering our proprietary technology and products. We also own or hold exclusive rights to foreign patents and patent applications corresponding to most of the U.S. patents and patent applications in our portfolio. Our issued patents include patents on Natrecor, certain of our p38 kinase inhibitors, FGF, VEGF121 and GLP-1. Our proprietary position with respect to certain principal products under development is described below. If a patent issues prior to marketing approval, as has been the case with all of our issued patents to date, we can apply for extension of the patent term for a limited period of time to make up for a portion of the patent term lost to the regulatory approval period. The absence of a patent covering products which we have licensed to third parties could reduce the royalties due to us under the agreements with those parties.

Natrecor. We have been issued United States, Canadian and European patents covering the endogenous form of Natrecor, human BNP. Our U.S. patents on Natrecor are subject to possible extension due to time taken up in the regulatory approval process. We believe our key patent on Natrecor, which currently expires in May 2009, may be extended to late 2013 or early 2014. Pursuant to an exclusive license granted to us by Shionogi & Co., Ltd., we also have the exclusive right to develop therapeutic products using BNP under certain patents and applications on BNP originally filed by Daiichi Pharmaceutical Co., Ltd. and subsequently acquired by Shionogi. Although we were granted a Japanese patent on BNP, the patent was revoked in 1998 in an opposition filed against the patent by an unidentified party. The opposition did not challenge the originality of our BNP discovery but based its challenge solely on an interpretation of utility requirements for patentability peculiar to Japanese patent law. We appealed the revocation to the Tokyo High Court. On March 13, 2001, the Tokyo high court affirmed the revocation. Because we believe the decision is contrary to both Japanese precedent and patentability requirements in the United States and Europe, we intend to appeal the revocation to the Japanese Supreme Court. The decision does not affect our patent rights outside of Japan, nor does the revocation impact our ability to exclusively market BNP in Japan insofar as our exclusive license under the patent rights of Daiichi includes several Japanese patents of Daiichi directed to BNP.

p38 kinase inhibitors. We have filed a series of patent applications in the United States covering the classes of p38 kinase inhibitors that we have identified. To date, we have been issued two U.S. patents directed to certain of these p38 inhibitors. These patents will expire in 2018, subject to possible extension for FDA regulatory delays. While the classes of small molecule compounds identified by our researchers appear to be unique, we are aware that other

companies are also working to develop p38 kinase inhibitor compounds, and have filed patent applications on and received patents covering certain classes of compounds that these competing companies have identified, and covering various aspects of identifying such compounds.

FGF. After an interference with The Salk Institute for Biological Studies, we were awarded a U.S. patent on DNA sequences, expression vectors, and microorganisms used in the recombinant production of human basic FGF. Our basic FGF patent will expire in 2012, and may be extended for FDA regulatory delays. We also hold European patents on human basic FGF. Synergen, Inc., now owned by Amgen Inc., has obtained patents directed to a form of FGF that we believe is different from the form of FGF produced by us. A U.S. patent issued to Salk contains claims directed to substantially pure mammalian basic FGF containing the 146 amino acid sequence of bovine basic FGF or a naturally occurring homologous sequence of another mammalian species. Although we have been advised by counsel that the Salk patent would be invalid if read broadly enough to cover our form of FGF, there is still risk that an assertion of this patent could block our partners' ability to develop and market human basic FGF in the absence of a license, or if such a license is granted, could reduce the royalty income to us. We successfully opposed Salk's European patent, the revocation of which is currently under appeal by Salk. Our European patent was opposed by Chiron and Pharmacia. Our patent was upheld and both opponents appealed. As a result of our license to Chiron, Chiron, who is also a licensee of Salk, withdrew from the opposition against our European patent, and we have withdrawn from our opposition against the Salk patent.

In March 1994, we obtained a non-exclusive license to make, use and sell FGF under a U.S. patent issued to Harvard University containing claims to purified cationic (basic) FGF. The Harvard patent is based on a patent application having a filing date earlier than the application which formed the basis for the Salk patent. Sublicense rights under this patent are included in the rights granted by us to our FGF licensees, Kaken and Chiron.

VEGF\\121\\. Seven isoforms of human VEGF (hVEGF) are known, having 121, 145, 148, 165, 183, 189 and 206 amino acids, respectively. We believe that our researchers were the first to identify, clone and produce by recombinant DNA technology the 121 amino acid form of hVEGF (hVEGF\\121\\). hVEGF\\121\\ is the only human VEGF isoform known not to bind to heparin. We own two U.S. patents issued in 1993 covering hVEGF\\121\\, and in 1996 received a European patent covering this VEGF isoform. Our U.S. patents on hVEGF121 will expire 2010 but may be extended for FDA regulatory delays. We have patent applications pending in Canada and Japan. Other companies and institutions, including Genentech, Inc., Pharmacia and the Regents of the University of California, hold patents and pending patent applications claiming various isoforms of hVEGF and certain VEGF variants.

Competition

For patients treated with acute CHF, many therapeutic options are available. Currently used drugs fall into three main categories: vasodilators,

inotropes and diuretics. Natrecor would compete against both vasodilators and inotropes in the acute CHF market. Many of these drugs are available in generic formulation and have an associated low cost. In addition, milrinone, an inotrope, is currently promoted by Sanofi-Synthelabo Inc. and is expected to lose patent protection in November 2001. We intend to price Natrecor above the cost of these existing drugs, which may harm our competitive position relative to these drugs. We may not be able to compete effectively with these long-standing existing forms of therapy.

New drugs in development for the treatment of acute CHF would compete with Natrecor if approved by the FDA or other regulatory agencies. Tezosentan, a non-selective endothelin receptor antagonist, is being developed by Actelion Ltd and is currently being used in Phase III clinical trials as a vasodilator for the treatment of acute CHF. Abbott had previously submitted an NDA for Simdax, a calcium sensitizer described as an inotrope, but withdrew the application in 2000. To our knowledge, Abbott has not announced its intent to refile an NDA for Simdax.

Current commercial competition for the inhibition of TNF in rheumatoid arthritis includes injectible proteins such as Johnson and Johnson's Remicade and Immunex Corporation's Enbrel. Current COX-2 inhibitors include Pharmacia's Celebrex and Merck & Co., Inc.'s Vioxx. In addition, many pharmaceutical companies have expressed

interest in pursuing the development of p38 kinase inhibitors. We are unable to determine if they are actively developing these compounds internally. If they are developing these or similar products, several of these companies possess both greater access to capital and research and development resources. We may be unable to compete effectively with any of these development projects. We are also aware that Vertex Pharmaceuticals is conducting Phase II clinical trials of its p38 kinase inhibitor compound. If we are successful in developing our own p38 kinase inhibitor compound we may face intense competition.

We expect that competition for our products, when approved for sale, will be based, among other things, on efficacy, reliability, product safety, price and patent position. Our ability to compete effectively and develop products that can be manufactured cost-effectively and marketed successfully will depend on our ability to:

- advance our technology platforms;
- license additional technology;
- maintain a proprietary position in our technologies and products;
- obtain required government and other public and private approvals on a timely basis;
- attract and retain key personnel; and
- enter into corporate partnerships.

Our failure to achieve any of the above goals could impair our business.

Government Regulation

Our industry is heavily regulated. Our research and development activities and the production and marketing of our products are subject to extensive regulation for safety and efficacy by numerous governmental authorities in the

United States and other countries. The procedure for seeking and obtaining the required governmental approvals for a new product involves many steps, beginning with animal testing to determine safety and potential toxicity. In addition, extensive human clinical testing is required to demonstrate the efficacy, optimal dose and safety of each product. The time and expense required to perform clinical testing can far exceed the time and expense of developing the product prior to clinical testing. Whether undertaken by us or our commercial partners, the process of seeking and obtaining these approvals for a new product is likely to take a number of years and involves the expenditure of substantial resources. In addition, there can be no assurance that any of our products will receive the necessary approvals on a timely basis, if at all.

Even if initial FDA approval is obtained for a product, further studies may be required to provide additional data or to gain approval for the use of a product as a treatment for clinical indications other than those initially targeted. Moreover, the FDA may reconsider its approval of any product at any time and may withdraw such approval. In addition, before our products can be marketed in foreign countries, they are subject to regulatory approval in such countries similar to that required in the United States. Accordingly, numerous factors will impact the timing, extent and value of any regulatory approvals that may be obtained for our products, including changes in regulatory requirements, which may either decrease or increase the burden on us, the level of side effects exhibited by our products as compared to their beneficial effects, the availability of adequate resources to regulatory agencies which will impact the speed of regulatory review, and the prices we are able to charge for our products.

FDA regulations require that any drug to be tested in humans must be manufactured according to current Good Manufacturing Practices, or cGMPs. The cGMPs set certain minimum requirements for procedures, record-keeping and the physical characteristics of the facilities used in the production of these drugs. In addition, various foreign and U.S. federal, state and local laws and regulations relating to safe working conditions, laboratory practices, the experimental use of animals, and the storage, use and disposal of hazardous or potentially hazardous substances, including

radioactive compounds and infectious disease agents, used in connection with our research and manufacturing work are or may be applicable to such activities. They include, among others, the United States Atomic Energy Act, the Clean Air Act, the Clean Water Act, the Occupational Safety and Health Act, the National Environmental Policy Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, national restrictions on technology transfer, import, export and customs regulations, and other present and possible future foreign, federal, state and local regulations.

Employees

We had 194 full-time employees as of December 31, 2000. As of December 31, 2000, we also employed 94 part-time field sales representatives whose employment has since been terminated in our psychiatric sales and marketing division.

RISK FACTORS

You should carefully consider the risks described below before making an investment decision. Our business, financial condition or results of operations could be harmed by any of these risks. The risks described below are not the

only ones facing our company. Additional risks not presently known to us or that we currently deem immaterial may also impair our business operations.

This document also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of the risks faced by us, including those described below and elsewhere in this document.

Risks Related to Natrecor (nesiritide)

If the U.S. Food and Drug Administration, or FDA, finds that our amended New Drug Application, or NDA, for Natrecor does not support approval for marketing, the commercialization of Natrecor may be delayed or prevented.

In April 1999, the FDA issued us a non-approval letter for Natrecor. To address the FDA's concerns, we conducted a Phase III clinical trial; and in January 2001, we submitted an amendment to our NDA seeking approval to market Natrecor in the United States. We are initially seeking FDA approval for use of Natrecor as a treatment for acute congestive heart failure, or acute CHF. The FDA may not find our clinical data adequate to support Natrecor as a treatment for acute CHF or any other disease. Moreover, the FDA may require us to commence and complete additional clinical trials to generate additional data to support product approval for the treatment of acute CHF, which may lead to a substantial delay in its approval of Natrecor or prevent Natrecor from being approved for any medical use.

If Natrecor does not gain market acceptance, our business will suffer.

Even if clinical trials demonstrate the safety and efficacy of Natrecor and the necessary regulatory approvals are obtained, Natrecor may not gain market acceptance among physicians, patients, healthcare payors and the medical community. We will need to educate doctors and other healthcare advisors of the safety and clinical efficacy of Natrecor and its potential advantages over other treatments. The degree of market acceptance of Natrecor will also depend on a number of factors, including:

- the degree of clinical efficacy and safety;
- cost-effectiveness of Natrecor;
- its advantage over alternative treatment methods; and
- reimbursement policies of government and third-party payors.

To the extent market acceptance of Natrecor is limited, our revenues may suffer.

If the FDA determines that our third-party manufacturing facilities are not adequate, either before or after receipt of FDA marketing approval, we may lose the ability to manufacture and sell Natrecor.

As part of the NDA approval process and periodically thereafter, the FDA is likely to inspect each of the facilities involved in manufacturing Natrecor. Natrecor is manufactured for us by Biochemie GmbH, a subsidiary of Novartis, in Austria and is shipped in powder form to Abbott Laboratories in McPherson, Kansas where it is blended, filled and packaged for shipment. Although each facility has previously passed FDA inspections, future inspections

may find deficiencies in the facilities or processes that may delay or prevent the manufacture or sale of Natrecor. Even if the FDA approves Natrecor for

marketing, the FDA will subsequently conduct periodic inspections of these manufacturing facilities and, if deficiencies are identified, we may lose the ability to supply and sell Natrecor for extended periods of time.

We rely on third-party manufacturers, and if they experience any difficulties with their manufacturing processes, we may not obtain sufficient quantities of Natrecor to assure availability.

We rely on third parties for the manufacture of bulk drug substances and final drug product for clinical and commercial purposes relating to Natrecor. Biochemie GmbH is responsible for manufacturing Natrecor in bulk quantities and Abbott Laboratories is responsible for blending, filling and packaging Natrecor, and if they encounter problems in these processes, our revenues from future sales of Natrecor could decrease. Natrecor is manufactured using industry accepted recombinant manufacturing techniques which must be conducted under strict controls and tight timelines. Natrecor is subject to strict quality control testing during all phases of production and prior to its release to the market. Any quality control testing failures could lead to a reduction in the available supply of Natrecor. Biochemie depends on outside vendors for the timely supply of raw materials used to produce our products, including Natrecor. Once a supplier's materials have been selected for use in Biochemie's manufacturing process, the supplier in effect becomes a sole or limited source of that raw material due to regulatory compliance procedures. We depend on these third parties to perform their obligations effectively and on a timely basis. If these third parties fail to perform as required, our ability to deliver Natrecor on a timely basis would be impaired.

In addition, in the event of a natural disaster, equipment failure, power failure, strike or other difficulty, we may be unable to replace our third party manufacturers in a timely manner and would be unable to manufacture Natrecor to meet market needs.

The success of Natrecor is highly dependent on our partner, Innovex L.P., a division of Quintiles Transnational Corp., for marketing, promotion and sales activities.

We believe that for Natrecor to be widely adopted, the efforts of an experienced sales force are needed. We have limited experience in managing or operating a marketing organization. Accordingly, we have entered into an exclusive agreement with Innovex to co-promote, sell and distribute Natrecor in the United States. As part of our agreement with Innovex, we intend to build a sales force of approximately 180 people solely dedicated to the sale of Natrecor. If Innovex and we fail to devote appropriate resources to promote, sell and distribute Natrecor, sales of Natrecor could be reduced. If Innovex breaches or terminates its agreement with us or otherwise fails to conduct its Natrecor-related activities in a timely manner or if there is a dispute about its obligations, we may need to seek another partner. In that event, we cannot assure you that we will be able to obtain another partner on favorable terms, if at all.

The failure of PharmaBio Development, Inc., an affiliate of Innovex, to fulfill its obligation to partially fund the commercialization of Natrecor may affect our ability to successfully market Natrecor.

PharmaBio has agreed to fund $30.0 million of our costs to launch Natrecor over the first 24 months of Natrecor's commercialization and to loan us up to $5.0 million. Of the $30.0 million, we anticipate that $10.0 million will be paid to us in 2001 following FDA approval of Natrecor. If PharmaBio breaches or terminates its agreement with us or otherwise fails to fulfill its financial obligations under the agreement and we are unable to secure alternative funding, we may lose our ability to successfully market Natrecor.

In the area of acute CHF, we face competition from companies with substantial financial, technical and marketing resources, which could limit our future revenues from Natrecor.

Many therapeutic options are available for patients with acute CHF. Currently used drugs fall into three main categories: vasodilators, inotropes and diuretics. Natrecor would compete against both vasodilators and inotropes in the acute CHF market. Many of these drugs are available in generic formulation with an associated low

cost. In addition, milrinone, an inotrope, is currently promoted by Sanofi-Synthelabo Inc. We may not be able to compete effectively with these long-standing current forms of therapy. In addition, we will price Natrecor above the cost of these existing drugs, which may harm our competitive position relative to these drugs.

New drugs in development for the treatment of acute CHF would also compete with Natrecor if approved by the FDA or other regulatory agencies. Tezosentan, a non-selective endothelin receptor antagonist, is being developed by Actelion Ltd and is currently being evaluated in Phase III clinical trials as a vasodilator for the treatment of acute CHF. In addition, Abbott had previously submitted an NDA for Simdax, a calcium sensitizer described as an inotrope, but withdrew the application in 2000. To our knowledge, Abbott has not announced its intent to refile an NDA for Simdax. If any such new drug in development is approved by the FDA or other regulatory agencies, we may not be able to compete effectively with these new forms of therapy.

If we fail to gain approval for Natrecor and our other product candidates in international markets, our market opportunities will be limited.

We have not yet filed for marketing clearance for the use of Natrecor or any other product candidates in foreign countries, and we may not be able to obtain any international regulatory approvals for Natrecor or any other product we develop. If we fail to obtain those approvals or if such approvals are delayed, the geographic market for Natrecor or our other product candidates would be limited.

We will require a partner to market and commercialize Natrecor and our other product candidates in international markets.

We plan to partner with other companies for the sale of Natrecor and our other product candidates outside of the United States. We cannot assure you that we will be able to enter into such arrangements on favorable terms or at all. In addition, partnering arrangements could result in lower levels of income to us than if we marketed our products entirely on our own. In the event that we are unable to enter into a partnering arrangement for Natrecor or our other product candidates in international markets, we cannot assure you we will be able to develop an effective international sales force to successfully market and commercialize those products. If we fail to enter into partnering arrangements for our products and are unable to develop an effective international sales force, our revenues would be limited.

If we fail to obtain additional marketing approvals from the FDA for the use of Natrecor for additional therapeutic indications or if after approval such approval is subsequently revoked, our revenues from Natrecor will suffer.

In order to expand the medical uses, or therapeutic indications, for which we may market Natrecor, we must successfully complete additional clinical trials which could be lengthy and expensive and will require the allocation of both

substantial management and financial resources. Thereafter, we will have to apply separately to the FDA for clearance to market Natrecor for other indications. We cannot assure you that we will be able to successfully complete the required clinical trials or that the FDA will approve Natrecor for any additional indications. In addition, even if Natrecor is approved by the FDA, we cannot exclude the possibility that serious adverse events related to the use of Natrecor might occur in the future, which could either limit its use or cause the FDA to revoke our approval to market Natrecor.

Other Risks Related to Scios

We have a history of losses, expect to operate at a loss for the foreseeable future and may never be profitable.

We may not be able to achieve or earn a profit in the future. We began operations in December 1981, and since that time, with the sole exception of 1983, we have not earned a profit on a full-year basis. Our losses have historically resulted primarily from our investments in research and development. As of December 31, 2000, we had an accumulated deficit of approximately $411.4 million.

To date, nearly all of our revenues have come from:

- one-time signing fees from our corporate partners under agreements supporting the research, development and commercialization of our product candidates;
- one-time payments from our corporate partners when we achieved regulatory or development milestones;
- research funding from our corporate partners; and
- our psychiatric sales and marketing division.

We expect that our research, development and clinical trial activities and regulatory approvals, together with future general and administrative activities and the costs associated with launching and commercializing our product candidates and launching and commercializing Natrecor in the United States, will result in significant expenses for the foreseeable future.

If we fail to obtain the capital necessary to fund our operations, we may have to delay or scale back some of our programs or grant rights to third parties to develop and market our products.

We will continue to expend substantial resources developing new and existing product candidates, including costs associated with research and development, acquiring new technologies, conducting preclinical studies and clinical trials, obtaining regulatory approvals and manufacturing products. We believe our current working capital and future payments, if any, from our collaboration arrangements will be sufficient to meet our operating and capital requirements for at least the next 12 months. Our need for additional funding depends on a number of factors including:

- higher costs and slower progress than expected in developing product candidates and obtaining regulatory approvals, particularly for Natrecor;
- acquisition of technologies and other business opportunities that require financial commitments; or

- lower revenues than expected from the commercialization of our potential products.

Additional funding may not be available to us on favorable terms, if at all. We may raise funds through public or private financings, collaborative arrangements or other arrangements. Debt financing, if available, may involve covenants which could restrict our business activities. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, scale back or eliminate expenditures for some of our development programs or grant rights to develop and market product candidates that we would otherwise prefer to develop and market internally. If we are required to grant such rights, the ultimate value of these product candidates to us may be reduced.

Our operating results are subject to fluctuations that may cause our stock price to decline.

Our revenues and expenses have fluctuated significantly in the past. This fluctuation has in turn caused our operating results to vary significantly from quarter to quarter and year to year. We expect the fluctuations in our revenues and expenses to continue, and thus, our operating results should also continue to vary significantly. These fluctuations may be due to a variety of factors including:

- the timing and realization of milestone and other payments from our corporate partners;

- the timing and amount of expenses relating to our research and development, product development and manufacturing activities; and

- the extent and timing of costs related to our activities to obtain patents on our inventions and to extend, enforce and/or defend our patents and other rights to our intellectual property.

Because of these fluctuations, it is possible that our operating results for a particular quarter or quarters will not meet the expectations of public market analysts and investors, causing the market price of our common stock to decline. We believe that period-to-period comparisons of our operating results are not a good indication of our future performance, and you should not rely on those comparisons to predict our future operating or share price performance.

We depend on our key personnel and we must continue to attract and retain key employees and consultants.

We depend on our key scientific and management personnel. Our ability to pursue the development of our current and future product candidates depends largely on retaining the services of our existing personnel and hiring additional qualified scientific personnel to perform research and development. We also rely on personnel with expertise in clinical testing, government regulation, manufacturing and marketing. Attracting and retaining qualified personnel will be critical to our success. We may not be able to attract and retain personnel on acceptable terms given the competition for such personnel among biotechnology, pharmaceutical and healthcare companies, universities and non-profit research institutions. Failure to retain our key scientific and management personnel or to attract additional highly-qualified personnel could delay the development of our product candidates and harm our business.

Other than Natrecor, our product candidates are at early stages of development,

and if we are unable to develop and commercialize these product candidates successfully, we will not generate revenues from these products.

To date, none of our product candidates has been commercialized. Other than Natrecor, all of our product candidates are in early stages of development. We face the risk of failure normally found in developing biotechnology products based on new technologies. Successfully developing, manufacturing, introducing and marketing our early-stage product candidates will require several years and substantial additional capital.

Our operations depend on compliance with complex FDA and comparable international regulations. If we fail to obtain approvals on a timely basis or to achieve continued compliance, the commercialization of our products could be delayed.

We cannot assure you that we will receive the regulatory approvals necessary to commercialize our product candidates, which could cause our business to fail. Our product candidates are subject to extensive and rigorous government regulation by the FDA and comparable agencies in other countries. The FDA regulates, among other things, the development, testing, manufacture, safety, efficacy, record-keeping, labeling, storage, approval, advertising, promotion, sale and distribution of biopharmaceutical products. If our potential products are marketed abroad, they will also be subject to extensive regulation by foreign governments. None of our lead product candidates has been approved for sale in the United States or any foreign market. In addition, we have only limited experience in filing and pursuing applications necessary to gain regulatory approvals, which may impede our ability to obtain such approvals.

The results of preclinical studies and clinical trials of our products may not be favorable.

In order to obtain regulatory approval for the commercial sale of any of our product candidates, we must conduct both preclinical studies and human clinical trials. These studies and trials must demonstrate that the product is safe and effective for the clinical use for which we are seeking approval. We are currently conducting Phase Ib clinical trials of our lead p38 kinase inhibitor small molecule compound. The results of these or other clinical trials that we may conduct in the future may not be successful. Adverse results from our current or any future trials would harm our business.

We also face the risk that we will not be permitted to undertake or continue clinical trials for any of our product candidates in the future. Even if we are able to conduct such trials, we may not be able to satisfactorily demonstrate that the products are safe and effective and thus qualify for the regulatory approvals needed to market and sell them. Results

from preclinical studies and early clinical trials are often not accurate indicators of results of later-stage clinical trials that involve larger human populations.

Our products use novel alternative technologies and therapeutic approaches which have not been widely studied.

Many of our product development efforts focus on novel alternative therapeutic approaches and new technologies that have not been widely studied. These approaches and technologies may not be successful. We are applying these approaches and technologies in our attempt to discover new treatments for conditions that are also the subject of research and development efforts of many other companies.

Rapid changes in technology and industry standards could render our potential products unmarketable.

We are engaged in a field characterized by extensive research efforts and rapid technological development. New drug discoveries and developments in our field and other drug discovery technologies are accelerating. Our competitors may develop technologies and products that are more effective than any we develop or that render our technology and potential products obsolete or noncompetitive. In addition, our potential products could become unmarketable if new industry standards emerge. To be successful, we will need to enhance our product candidates and design, develop and market new product candidates that keep pace with new technological and industry developments.

Many other companies are targeting the same diseases and conditions as we are. Competitive products from other companies could significantly reduce the market acceptance of our products.

The markets in which we compete are well-established and intensely competitive. We may be unable to compete successfully against our current and future competitors. Our failure to compete successfully may result in pricing reductions, reduced gross margins and failure to achieve market acceptance for our potential products. Our competitors include pharmaceutical companies, biotechnology companies, chemical companies, academic and research institutions and government agencies.

For example, many pharmaceutical and biotechnology companies have initiated research programs similar to ours. Many of these organizations have substantially more experience and more capital, research and development, regulatory, manufacturing, sales, marketing, human and other resources than we do. As a result, they may:

- develop products that are safer or more effective than our product candidates;
- obtain FDA and other regulatory approvals or reach the market with their products more rapidly than we can, reducing the potential sales of our product candidates;
- devote greater resources to market or sell their products;
- adapt more quickly to new technologies and scientific advances;
- initiate or withstand substantial price competition more successfully than we can;
- have greater success in recruiting skilled scientific workers from the limited pool of available talent;
- more effectively negotiate third-party licensing and collaboration arrangements; and
- take advantage of acquisition or other opportunities more readily than we can.

In addition, our product candidates, if approved and commercialized, will compete against well-established existing therapeutic products that are currently reimbursed by government health administration authorities, private health insurers and health maintenance organizations. We face and will continue to face intense competition from other companies for collaborative arrangements with pharmaceutical and biotechnology companies, for relationships with

academic and research institutions and for licenses to proprietary technology. In addition, we anticipate that we will face increased competition in the future as new companies enter our markets and as scientific developments continue to expand the understanding of various diseases. While we will seek to expand our technological capabilities to remain competitive, research and development by others may render our technology or product candidates obsolete or noncompetitive or result in treatments or cures superior to any therapy developed by us.

If we are unable to protect our intellectual property rights adequately, the value of our potential products could be diminished.

Our success is dependent in part on obtaining, maintaining and enforcing our patents and other proprietary rights. Patent law relating to the scope of claims in the biotechnology field in which we operate is still evolving and surrounded by a great deal of uncertainty. Accordingly, we cannot assure you that our pending patent applications will result in issued patents. Because certain U.S. patent applications may be maintained in secrecy until a patent issues, we cannot assure you that others have not filed patent applications for technology covered by our pending applications or that we were the first to invent the technology.

Other companies, universities and research institutions have or may obtain patents and patent applications that could limit our ability to use, manufacture, market or sell our product candidates or impair our competitive position. As a result, we may have to obtain licenses from other parties before we could continue using, manufacturing, marketing or selling our potential products. Any such licenses may not be available on commercially acceptable terms, if at all. If we do not obtain required licenses, we may not be able to market our potential products at all or we may encounter significant delays in product development while we redesign potentially infringing products or methods.

In addition, although we own a number of patents, including issued patents and patent applications relating to Natrecor and certain of our p38 kinase inhibitors, the issuance of a patent is not conclusive as to its validity or enforceability, and third parties may challenge the validity or enforceability of our patents. We cannot assure you how much protection, if any, will be given to our patents if we attempt to enforce them and they are challenged in court or in other proceedings. It is possible that a competitor may successfully challenge our patents or that challenges will result in limitations of their coverage. In addition, the cost of litigation to uphold the validity of patents can be substantial. If we are unsuccessful in such litigation, third parties may be able to use our patented technologies without paying licensing fees or royalties to us.

Moreover, competitors may infringe our patents or successfully avoid them through design innovation. To prevent infringement or unauthorized use, we may need to file infringement claims, which are expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or may refuse to stop the other party from using the technology at issue on the grounds that its technology is not covered by our patents. Policing unauthorized use of our intellectual property is difficult, and we cannot assure you that we will be able to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States.

In addition to our patented technology, we also rely on unpatented technology, trade secrets and confidential information. We may not be able to

effectively protect our rights to this technology or information. Other parties may independently develop substantially equivalent information and techniques or otherwise gain access to or disclose our technology. We require each of our employees, consultants and corporate partners to execute a confidentiality agreement at the commencement of an employment, consulting or collaborative relationship with us. However, these agreements may not provide effective protection of our technology or information or, in the event of unauthorized use or disclosure, they may not provide adequate remedies.

If we fail to negotiate or maintain successful arrangements with third parties, our development and marketing activities may be delayed or reduced.

We have entered into, and we expect to enter into in the future, arrangements with third parties to perform

research, development, regulatory compliance, manufacturing or marketing activities relating to some or all of our product candidates. If we fail to secure or maintain successful collaborative arrangements, our development and marketing activities may be delayed or reduced. We may be unable to negotiate favorable collaborative arrangements that, if necessary, modify our existing arrangements on acceptable terms.

Most of our agreements can be terminated under certain conditions by our partners. In addition, our partners may separately pursue competing products, therapeutic approaches or technologies to develop treatments for the diseases targeted by us or our efforts. Even if our partners continue their contributions to the collaborative arrangements, they may nevertheless determine not to actively pursue the development or commercialization of any resulting products. Also, our partners may fail to perform their obligations under the collaborative arrangements or may be slow in performing their obligations. In these circumstances, our ability to develop and market potential products could be severely limited.

Risks Related to our Industry

We face uncertainties over reimbursement and healthcare reform.

In both domestic and foreign markets, future sales of our potential products, if any, will depend in part on the availability of reimbursement from third-party payors such as government health administration authorities, private health insurers and other organizations. Third-party payors are increasingly challenging the price and cost-effectiveness of medical products and services. Significant uncertainty exists as to the reimbursement status of newly-approved health care products. Even if we were to obtain regulatory approval, our product candidates may not be considered cost-effective and adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investments in product development. Legislation and regulations affecting the pricing of pharmaceuticals may change before any of our product candidates is approved for marketing. Adoption of such legislation and regulations could further limit reimbursement for medical products and services. If the government and third-party payors fail to provide adequate coverage and reimbursement rates for our potential products, the market acceptance of our products may be adversely affected.

We may be required to defend lawsuits or pay damages in connection with the alleged or actual harm caused by our product candidates.

We face an inherent business risk of exposure to product liability claims

in the event that the use of our product candidates is alleged to have resulted in harm to others. This risk exists in clinical trials as well as in commercial distribution. In addition, the pharmaceutical and biotechnology industries in general have been subject to significant medical malpractice litigation. We may incur significant liability if product liability or malpractice lawsuits against us are successful. Although we maintain product liability insurance, we cannot be sure that this coverage is adequate or that it will continue to be available to us on acceptable terms.

We use hazardous materials in our business, and any claims relating to improper handling, storage or disposal of these materials could harm our business.

Our research and development activities involve the controlled use of hazardous materials, chemicals, biological agents and radioactive compounds. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of such materials and certain waste products. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by such laws and regulations, the risk of accidental contamination or injury from these materials cannot be completely eliminated. In the event of such an accident, we could be held liable for any resulting damages, and any such liability could exceed our resources. We may be required to incur significant costs to comply with these laws in the future. Failure to comply with these laws could result in fines and the revocation of permits, which could prevent us from conducting our business.

Our stock price continues to experience large fluctuations, and you could lose some or all of your investment.

The market price of our stock has been and is likely to continue to be highly volatile. These price fluctuations have been rapid and severe. The market price of our common stock may fluctuate significantly in response to the following factors, most of which are beyond our control:

- variations in our quarterly operating results;
- changes in securities analysts' estimates of our financial performance;
- changes in market valuations of similar companies;
- announcements by us or our competitors of significant contracts,
- acquisitions, strategic partnerships, joint ventures or capital commitments;
- additions or departures of key personnel;
- future sales of common stock;
- announcements by us or our competitors of technological innovations of new therapeutic products, clinical trial results and developments in patent or other proprietary rights;
- announcements regarding government regulations, public concern as to the safety of drugs developed by us or others or changes in reimbursement policies; and
- fluctuations in stock market price and volume, which are particularly

common among securities of biopharmaceutical companies.

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced greater than average stock price volatility in recent years. Several years ago, we were the subject of a securities class action lawsuit, which was eventually dismissed with a determination that the plaintiffs had no basis for their claim. If we face such litigation in the future, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We have implemented provisions in our charter documents that may ultimately delay, discourage or prevent a change in our management or control of us.

Our certificate of incorporation and bylaws contain provisions that could make it more difficult for our stockholders to replace or remove our directors or to effect any other corporate action. These provisions include those which:

- prohibit holders of less than ten percent of our outstanding capital stock from calling special meetings of stockholders;
- prohibit stockholder action by written consent, thereby requiring stockholder actions to be taken at a meeting of our stockholders; and
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters than can be acted upon by stockholders at stockholder meetings.

Moreover, our certificate of incorporation does not provide for cumulative voting in the election of directors, which would otherwise allow less than a majority of stockholders to elect director candidates.

Some of the above provisions may also have possible anti-takeover effects, which may make an acquisition of us by a third party more difficult, even if such an acquisition could be beneficial to our stockholders. In addition, our certificate of incorporation also authorizes us to issue up to 20,000,000 shares of preferred stock in one or more different series with terms to be determined by our board of directors at time of issuance. As of December 31, 2000, an aggregate of 71,053 shares of preferred stock had been authorized for issuance by the board of directors and 4,991 shares were issued and outstanding. Issuance of other shares of preferred stock could also be used as an anti-takeover device.

MANAGEMENT

Executive Officers

Our executive officers and their ages at January 30, 2001 are as follows:

Name	Age	Position
Richard B. Brewer.....	49	President, Chief Executive Officer and Director
George F. Schreiner, M.D.....	51	Chief Scientific Officer

David W. Gryska.....	44	Senior Vice President, Finance and Chief Financial Officer
John H. Newman.....	50	Senior Vice President, General Counsel and Secretary
Patricia Baldwin, Ph.D.....	45	Vice President, Quality and Product Development
Thomas L. Feldman.....	50	Vice President, Sales and Marketing
Darlene P. Horton, M.D.....	39	Vice President, Medical Affairs

Richard B. Brewer joined Scios in September 1998 as President, Chief Executive Officer and Director on our Board of Directors. From February 1996 to June 1998, he served as our Executive Vice President of Operations and then Chief Operating Officer of Heartport, Inc., a medical device company. From 1984 to 1995, Mr. Brewer served in various capacities for Genentech Europe Ltd., Genentech Canada, Inc. and Genentech, Inc., most recently as Senior Vice President, U.S. Sales and Marketing. Mr. Brewer holds a B.S. from Virginia Polytechnic Institute and a M.B.A. from Northwestern University.

Dr. George F. Schreiner joined Scios in January 1997 as Vice President, Cardiorenal Research. He became our Chief Scientific Officer in August 2000, responsible for leading our research group. From 1980 to 1992, Dr. Schreiner served on the faculties of Harvard Medical School and Washington University School of Medicine and in 1993 joined CV Therapeutics, Inc., a biopharmaceutical company, as Vice President, Medical Science and Preclinical Research. Dr. Schreiner holds an M.D. from Harvard Medical School and a Ph.D. in Immunology from Harvard University.

David W. Gryska joined Scios in December 1998 as Vice President of Finance and Chief Financial Officer and became our Senior Vice President of Finance in November 2000. From 1993 to December 1998, Mr. Gryska was Vice President, Finance and Chief Financial Officer of Cardiac Pathways Corporation, a medical device company. Mr. Gryska was with Ernst & Young LLP from 1982 to 1993 and served as a partner from 1989-1993.

John H. Newman joined Scios in 1983 as Vice President, General Counsel and Secretary, and became our Vice President of Commercial Development, General Counsel and Secretary in 1989, our Vice President of Legal Affairs, General Counsel and Secretary in 1992 and our Senior Vice President, General Counsel and Secretary in February 1998. Prior to joining Scios, Mr. Newman was an attorney in private practice.

Dr. Patricia Baldwin joined Scios in 1986 as a Scientist in the Novel Drug Delivery Department. In 1990, she

moved to the Pharmaceutical Research and Development Department and in 1995, Dr. Baldwin became our Director of Analytical Chemistry. In September 1999, she became our Senior Director of Analytical Methods and Quality Control and then, in March 2000, Dr. Baldwin was promoted to our Vice President, Quality and Product Development. Dr. Baldwin received a B.S. in Chemistry from Stanford University and a Ph.D. in Chemistry from University of California, Berkeley.

Thomas L. Feldman joined Scios in 1995 as Vice President of Commercial Operations and in November 1999, became our Vice President, Sales and Marketing. Prior to joining Scios, Mr. Feldman was responsible for sales and marketing activities at pharmaceutical companies affiliated with Johnson & Johnson. From 1993 through 1994, Mr. Feldman was National Sales Manager at Ortho Pharmaceutical Corporation. From 1973 to 1993, Mr. Feldman held various sales and marketing positions at McNeil Pharmaceutical, where he most recently served as National Sales Manager from 1990 to 1993.

Dr. Darlene P. Horton joined Scios in July 1996 and is responsible for

directing and managing our clinical research programs. In August 2000, Dr. Horton was appointed our Vice President, Medical Affairs. Prior to joining Scios, she was a Pediatric Cardiology Fellow at UCSF's Cardiovascular Research Institute, and she remains on the clinical faculty at the University of California, San Francisco. Dr. Horton received a B.S. in Microbiology and an M.D. from the University of Florida in Gainesville.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

SCIOS INC.

Date: May 29, 2001 By: /s/ Richard B. Brewer

Richard B. Brewer
President and Chief Executive Officer