ATHEROGENICS INC
Form 10-K/A
May 06, 2005

Table of Contents

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

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Form 10-K/A

(Amendment No. 2)

(Mark One)

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

For the fiscal year ended December 31, 2004

OR

o **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 0-31261

AtheroGenics, Inc.

(Exact name of Registrant as specified in its charter)

Georgia	**58-2108232**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification Number)*
8995 Westside Parkway, Alpharetta, Georgia 30004	**(678) 336-2500**
(Address of principal executive offices, including zip code)	*(Registrant s telephone number, including area code)*

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

None

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

Common Stock, No Par Value
Common Stock Purchase 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 þ No o

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

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

The aggregate market value of shares of voting stock held by nonaffiliates of the registrant, computed by reference to the closing price of $19.03 as reported on the Nasdaq National Market as of the last business day of AtheroGenics most recently completed second fiscal quarter (June 30, 2004), was approximately $422,239,543. AtheroGenics has no nonvoting common equity.

The number of shares outstanding of the registrant s common stock, as of March 8, 2005: 37,668,445.

Documents Incorporated by Reference:

Portions of the proxy statement filed pursuant to Regulation 14A under the Securities Exchange Act of 1934 with respect to the 2005 Annual Meeting of Shareholders are incorporated herein by reference in Part III.

Table of Contents

EXPLANATORY NOTE

AtheroGenics, Inc. is filing this Amendment No. 2 to its Annual Report on Form 10-K for the fiscal year ended December 31, 2004 to supplement the disclosure under Part II Item 7. Management s Discussion and Analysis of Financial Conditions and Results of Operations, as well as to correct certain typographical errors. This Amendment No. 2 includes the full text of our Annual Report on Form 10-K, including the information in Amendment No. 1 to the Annual Report on Form 10-K, filed on April 6, 2005. In addition, Item 15 includes the certifications required pursuant to Rules 13a-14(a)/15d-14(a) and 13a-14(b)/15d-14(b) of the Securities and Exchange Act of 1934, as amended (the Exchange Act), which have been re-executed and re-filed as of the date of this Amendment as Exhibits 31.5, 31.6 and 32.1, respectively.

With the exception of the foregoing, no other information in the Annual Report on Form 10-K for the fiscal year ended December 31, 2004 has been supplemented, updated or amended.

ATHEROGENICS, INC
FORM 10-K

INDEX

Table of Contents

PART I

Item 1. *Business*

Overview

AtheroGenics is a research-based pharmaceutical company incorporated in the State of Georgia in 1993. We are focused on the discovery, development and commercialization of novel drugs for the treatment of chronic inflammatory diseases, including coronary heart disease, organ transplant rejection, rheumatoid arthritis and asthma. We have developed a proprietary vascular protectant, or v-protectant®, technology platform to discover drugs to treat these types of diseases. Based on our v-protectant® platform, we have two drug development programs in clinical trials and are pursuing a number of other preclinical programs.

AGI-1067 is our v-protectant® candidate that is most advanced in clinical development. AGI-1067 is designed to benefit patients with coronary heart disease, or CHD, which is atherosclerosis of the blood vessels of the heart. Atherosclerosis is a common disease that results from inflammation and the buildup of plaque in arterial blood vessel walls. Nearly 13 million people in the United States currently have diagnosed CHD. There are no medications available for physicians to treat directly the underlying chronic inflammation associated with CHD. Instead, physicians treat risk factors, such as high cholesterol and high blood pressure, to slow the progression of the disease. The anti-inflammatory mechanism of AGI-1067 represents a novel, direct therapeutic approach that may be suitable as a chronic treatment for all patients with CHD, including those without traditional risk factors.

In November 2004, we completed a Phase IIb clinical trial called CART-2, a 465-patient study that examined the effect of 12 months of AGI-1067 therapy on atherosclerosis and post-angioplasty restenosis. Two leading cardiac intravascular ultrasound laboratories independently analyzed the final data from CART-2. The primary endpoint of the trial was a change in coronary atherosclerosis, measured as total plaque volume after a 12-month treatment period compared to baseline values. Combined results of the final analysis from the two laboratories, which were based on an evaluation of intravascular ultrasounds from approximately 230 patients in the study, indicate that AGI-1067 reduced plaque volume by an average of 2.3%, which was statistically significant. Results from the patient group receiving both placebo and standard of care indicated a plaque volume measure that was not statistically different from baseline. While the plaque regression observed in the AGI-1067 group exceeded that observed in the standard of care group numerically, the difference did not reach statistical significance, although a trend towards significance was seen in one laboratory s analysis. An important secondary endpoint from the trial, change in plaque volume in the most severely diseased subsegment, showed statistically significant regression from baseline by an average of 4.8%. The results also demonstrated a significant reduction in myeloperoxidase, an inflammatory biomarker that correlates with future cardiovascular events. Overall adverse event rates were similar in the AGI-1067 and standard of care groups, and AGI-1067 was generally well tolerated.

Based on the results of an End of Phase II meeting with the U.S. Food and Drug Administration, or FDA, we proceeded to develop a pivotal Phase III clinical trial protocol to evaluate AGI-1067 for the treatment of atherosclerosis. The Phase III protocol received a Special Protocol Assessment from the FDA in March 2003. A Special Protocol Assessment is written confirmation from the FDA that the protocol is adequately designed to support a New Drug Application for the drug in the specified treatment area.

In 2003, we initiated the pivotal Phase III trial, referred to as ARISE (Aggressive Reduction of Inflammation Stops Events), which is being conducted in cardiac centers in the United States, Canada, the United Kingdom and South Africa. ARISE will evaluate the impact of AGI-1067 on important outcome measures such as death due to coronary disease, myocardial infarction, stroke, coronary re-vascularization and unstable angina in patients who have CHD. The study will assess the incremental benefits of AGI-1067 versus the current standard of care therapies in this patient

population. As such, all patients in the trial, including those on placebo, will be receiving other appropriate heart disease medications, including statins and other cholesterol-lowering therapies, high blood pressure medications and anti-clotting agents.

We originally planned to enroll in ARISE 4,000 patients who would be followed for an average of 18 months or until a minimum of 1,160 primary events, or outcome measures, had occurred. In February 2005, we announced that the FDA approved our proposed amendment to the ARISE Phase III clinical trial protocol. The changes to the ARISE protocol are intended to enhance the trial as well as to accelerate its pace without affecting the Special Protocol Assessment with the FDA. The changes approved by the FDA include our plan to increase the number of patients in the study to a target of 6,000, eliminate the minimum 12 month follow-up period for patients and decrease the minimum number of primary events to 990. With these modifications, we would expect to complete enrollment by mid-2005 and complete the ARISE trial by the end of the first quarter of 2006. We then plan to file a New Drug Application with the FDA as soon as possible after we complete the trial and analyze the results.

Table of Contents

We previously were developing AGIX-4207, a v-protectant® candidate for the treatment of rheumatoid arthritis. Based on our findings, however, we have discontinued clinical development of AGIX-4207 and the intravenous dosage form of AGIX-4207 for rheumatoid arthritis. We continue to have an active program aimed at investigating other v-protectants® in rheumatoid arthritis and have identified other compounds with enhanced therapeutic potential within our rheumatoid arthritis preclinical models. We are working to select another candidate to move into formal preclinical development.

We have also identified additional potential v-protectant® candidates to treat other chronic inflammatory diseases, including asthma. We are evaluating these v-protectants® to determine lead drug candidates for clinical development. We plan to develop these compounds rapidly and may seek regulatory fast track status, if available, to expedite development and commercialization. We will continue to expand upon our v-protectant® technology platform using functional genomics to identify novel therapeutic gene targets. Functional genomics is the process by which one uses scientific models and techniques to discover and modify genes, measure the consequences of the modifications, and reliably determine the function of those genes.

Business Strategy

Our objective is to become a leading pharmaceutical company focused on discovering, developing and commercializing novel drugs for the treatment of chronic inflammatory diseases. The key elements of our strategy include the following:

Continue aggressive development program for AGI-1067. We intend to rapidly develop AGI-1067 for the treatment and prevention of atherosclerosis in patients with coronary heart disease. We are continuing to enroll patients in the ARISE Phase III clinical trial for the treatment of atherosclerosis in patients with coronary heart disease.

Extend our v-protectant® technology platform into additional therapeutic areas that address unmet medical needs. We believe that our v-protectants® have the potential for treating a wide variety of other chronic inflammatory diseases. These indications include chronic organ transplant rejection, rheumatoid arthritis, asthma and other diseases. We completed a Phase I clinical trial with positive results for AGI-1096, a v-protectant® developed for the prevention of chronic organ transplant rejection.

Expand our clinical product candidate portfolio. In addition to our existing discovery programs, we intend to acquire rights to other product candidates and technologies that complement our existing product candidate lines or that enable us to capitalize on our scientific and clinical development expertise. We plan to expand our product candidate portfolio by in-licensing or acquiring product candidates, technologies or companies.

Commercialize our products. We plan to collaborate with large pharmaceutical companies to commercialize products that we develop to target patient or physician populations in broad markets, such as AGI-1067 for atherosclerosis. In contrast, we plan to develop a sales force to commercialize those of our products that we develop to target appropriate patient or physician populations in narrow markets.

Inflammation and Disease

Inflammation is a normal response of the body to protect tissues from infection, injury or disease. The inflammatory response begins with the production and release of chemical agents by cells in the infected, injured or diseased tissue. These agents cause redness, swelling, pain, heat and loss of function. Inflamed tissues generate additional signals that recruit white blood cells to the site of inflammation. White blood cells destroy any infective or injurious agent, and remove cellular debris from damaged tissue. This inflammatory response usually promotes healing but, if uncontrolled, may become harmful.

The inflammatory response can be either acute or chronic. Acute inflammation lasts at most only a few days. The treatment of acute inflammation, where therapy includes the administration of aspirin and other non-steroidal anti-inflammatory agents, provides relief of pain and fever for patients. In contrast, chronic inflammation lasts weeks, months or even indefinitely and causes tissue damage. In chronic inflammation, the inflammation becomes the problem rather than the solution to infection, injury or disease. Chronically inflamed tissues continue to generate signals that attract white blood cells from the bloodstream. When white blood cells migrate from the bloodstream into the tissue they amplify the inflammatory response. This chronic inflammatory response can break down healthy tissue in a misdirected attempt at repair and healing. Diseases characterized by chronic inflammation include, among others:

Table of Contents

atherosclerosis, including coronary heart disease;

organ transplant rejection;

rheumatoid arthritis; and

asthma.

Atherosclerosis is a common cardiovascular disease that results from inflammation and the buildup of plaque in arterial blood vessel walls. Plaque consists of inflammatory cells, cholesterol and cellular debris. Atherosclerosis, depending on the location of the artery it affects, may result in a heart attack or stroke.

Atherosclerosis of the blood vessels of the heart is called coronary artery disease or heart disease. It is the leading cause of death in the United States, claiming more lives each year than all forms of cancer combined. Recent estimates suggest that over 13 million Americans are diagnosed with some form of atherosclerosis. When atherosclerosis becomes severe enough to cause complications, physicians must treat the complications themselves, including angina, heart attack, abnormal heart rhythms, heart failure, kidney failure, stroke, or obstructed peripheral arteries. Many of the patients with established atherosclerosis are treated aggressively for their associated risk factors, as with statins, which have been repeatedly shown to slow the progression of atherosclerosis and prevent future adverse events such as heart attack, stroke, and death. Other risk factors associated with atherosclerosis include elevated triglyceride levels, high blood pressure, smoking, diabetes, obesity and physical inactivity. Many atherosclerosis patients also experience symptoms of angina and/or a history of acute coronary syndromes, such as myocardial infarctions and unstable angina. In addition, most of these patients have high-cholesterol, and as a result, the current treatment focuses primarily on cholesterol reduction. Additionally, these patients are routinely treated with anti-hypertensives and anti-platelet drugs to help prevent the formation of blood clots. There are currently no medications available for physicians to treat directly the underlying chronic inflammation of atherosclerosis.

Organ transplantation takes place when an organ from a donor is surgically removed and placed in a recipient patient whose own organ has failed because of disease or infection. Except for transplants between identical twins, all transplant donors and recipients are immunologically incompatible. This biological incompatibility is a barrier that causes the recipient s immune system to try to destroy or reject the new organ. A patient s white blood cells produce special proteins called antibodies that are created specifically to latch onto the transplanted organ. While attached to the organ, the antibodies alert the rest of the immune system to attack the organ slowly and continuously. The current treatment for prevention of organ transplant rejection focuses on the use of powerful immunosuppressive drugs such as cyclosporin A, tacrolimus and rapamycin (sirolimus). These drugs, which are initiated during the acute rejection phase, need to be taken continuously after the transplant procedure, often cause side effects, and may fail to prevent long-term rejection of the transplant. Immunosuppressants may also impair the recipient s immune system in order to reduce the immune response against the transplant. The Scientific Registry of Transplant Recipients reports that even with the use of immunosuppressants, patients run the risk of losing a donated organ during the first three years following transplantation, and roughly 50 percent of patients have functioning organ transplants after approximately ten years.

Rheumatoid arthritis is a common form of arthritis that is characterized by inflammation of the membrane lining the joint, which causes pain, stiffness, warmth, redness and swelling. The inflamed joint lining, the synovium, can invade and damage bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement. When the immune system works properly, it is the body s defense against bacteria, viruses and other foreign cells. In an immune disorder like rheumatoid arthritis, the immune system works improperly and attacks the body s own joints and other organs. In rheumatoid arthritis, white blood cells move from the bloodstream into the joint tissues. Fluid containing inflamed cells accumulates in the joint. The white cells in the joint tissue and fluid produce many substances, including

enzymes, antibodies and other molecules that attack the joint and can cause damage. In the United States, approximately one percent of the population, or 2.1 million people, have rheumatoid arthritis. The cause of rheumatoid arthritis is not yet known, and the disease differs from person to person. Anyone can get rheumatoid arthritis, including children and the elderly. However, the disease usually begins in the young- to middle-adult years. Among people with rheumatoid arthritis, women outnumber men three-to-one. The disease occurs in all ethnic groups and in all parts of the world.

Current treatment methods for rheumatoid arthritis focus on relieving pain, reducing inflammation, stopping or slowing joint damage, and improving patient function and well-being, and include non-steroidal anti-inflammatory drugs, corticosteroids, and drugs designed to slow the progression of disease, termed disease modifying anti-rheumatic drugs, or DMARDs. DMARDs can cause

Table of Contents

serious side effects, and include drugs that were originally designed to treat cancer, such as methotrexate. Modern treatments with DMARDs developed by other companies, Enbrel® (etanercept) and Remicade® (infliximab), have substantially improved the quality of life for people with rheumatoid arthritis. These drugs prove that blocking the activity of tumor necrosis factor, a molecule that stimulates a broad range of cellular activities implicated in the inflammation process, improves rheumatoid arthritis. However, both of these drugs must be injected and both increase the risk of severe infection.

Asthma is a common chronic inflammatory disease of the bronchial tubes, which are the airways in the lungs. Asthma is marked by episodic airway attacks that are caused by many stresses, including allergy, cold air, ozone or exercise. Asthma therapy has concentrated on the use of inhaled corticosteroids to reduce chronic inflammation and bronchodilators to provide symptomatic relief. Asthmatic patients, however, continue to experience flare-ups, or exacerbations, that are not prevented nor effectively treated by these medicines.

Many physicians are only now becoming aware of the key role of chronic inflammation in diverse diseases such as atherosclerosis and asthma for which existing anti-inflammatory treatments are incomplete and limited in use. As more physicians recognize that a wide range of chronic diseases are inflammatory in nature, we believe that these physicians will require safer and more effective anti-inflammatory treatments. We believe that one of these therapeutic approaches will be the administration of drugs designed to block the migration of white blood cells through blood vessel walls into inflamed tissues, unless the inflammation is due to infection.

V-Protectant® Technology

We have developed a proprietary v-protectant® technology platform for the treatment of chronic inflammatory diseases. This platform is based on the work of our scientific co-founders R. Wayne Alexander, M.D., Ph.D. and Russell M. Medford, M.D., Ph.D. In 1993, Drs. Alexander and Medford discovered a novel mechanism within arterial blood vessel walls that could control the excessive accumulation of white blood cells without affecting the body s ability to fight infection. V-protectant® technology exploits the observation that the endothelial cells that line the interior wall of the blood vessel play an active role in recruiting white blood cells from the blood to the site of chronic inflammation. V-protectants® are drugs that block harmful effects of oxygen and other similar molecules, collectively called oxidants. Scientists have known for some time that some oxidants can damage cells, but have more recently determined that these same oxidants may also act as signals to modify gene activity inside cells. This change in gene activity leads to the production of proteins that initiate or maintain inflammation. The protein products of these cells, including VCAM-1, attract white blood cells to the site of chronic inflammation. We believe that an excess number of VCAM-1 molecules on the surface of cells is a disease state. We also believe that AGI-1067 and other v-protectants® can act as antioxidants and can block the specific type of inflammation caused by oxidants acting as signals. We believe that v-protectants® will provide this anti-inflammatory benefit without undermining the body s ability to protect itself against infection.

Products

The table below summarizes our therapeutic programs, their target indication or disease and their development status.

Therapeutic Program	Disease/Indication	Development Status
V-PROTECTANTS®		
AGI-1067	Atherosclerosis	Phase III clinical trial
AGI-1096		Phase I clinical trial

	Transplant rejection	
AGI Series	Chronic asthma	Pre-IND
AGI Series	Rheumatoid arthritis	Pre-IND
FUNCTIONAL GENOMICS PROGRAM	Inflammatory diseases	Research
MEKK TECHNOLOGY PLATFORM	Inflammatory diseases	Research

We have established therapeutic programs for product development using lead candidates we select from among our compound libraries. These programs seek to exploit the value of the products early and to expand their use broadly. We continue to test compounds to identify back-up and second-generation product candidates. We are also pursuing novel discovery targets in chronic inflammation.

Table of Contents

AGI-1067

AGI-1067 is our v-protectant® candidate that is most advanced in clinical development. AGI-1067 is designed to benefit patients with coronary heart disease, or CHD, which is atherosclerosis of the blood vessels of the heart. Atherosclerosis is a common disease that results from inflammation and the buildup of plaque in arterial blood vessel walls. Nearly 13 million people in the United States currently have diagnosed CHD. There are no medications available for physicians to treat directly the underlying chronic inflammation associated with CHD. Instead, physicians treat risk factors, such as high cholesterol and high blood pressure, to slow the progression of the disease. The anti-inflammatory mechanism of AGI-1067 represents a novel, direct therapeutic approach that may be suitable as a chronic treatment for all patients with CHD, including those without traditional risk factors.

We completed a 305-patient Phase II clinical trial of AGI-1067 called CART-1 (Canadian Antioxidant Restenosis Trial) in May 2001. Results from the trial showed that the study met its primary endpoint, which was improvement in the size of the luminal area, or coronary artery opening, as measured by intravascular ultrasound six months after angioplasty, with statistical significance. CART-1 data also showed that after only six weeks of therapy, there was an apparent anti-atherosclerotic effect in blood vessels adjacent to the angioplasty site, but not involved in the angioplasty. In the trial, AGI-1067 was well tolerated, with no increase in serious adverse events versus placebo. In January 2004, we performed an analysis of CART-1 data that provided additional information on the impact of AGI-1067 on plaque burden, a measure of disease in coronary vessels. In the treatment groups in CART-1 receiving the two highest doses of AGI-1067, plaque burden decreased by 1.6% and 1.9%, a therapeutic effect that we believe is consistent with reversing coronary artery disease.

In November 2004, we completed a Phase IIb clinical trial called CART-2, a 465-patient study that examined the effect of 12 months of AGI-1067 therapy on atherosclerosis and post-angioplasty restenosis. Two leading cardiac intravascular ultrasound laboratories independently analyzed the final data from CART-2. The primary endpoint of the trial was a change in coronary atherosclerosis, measured as total plaque volume after a 12-month treatment period compared to baseline values. Combined results of the final analysis from the two laboratories, which were based on an evaluation of intravascular ultrasounds from approximately 230 patients in the study, indicate that AGI-1067 reduced plaque volume by an average of 2.3%, which was statistically significant. Results from the patient group receiving both placebo and standard of care indicated a plaque volume measure that was not statistically different from baseline. While the plaque regression observed in the AGI-1067 group exceeded that observed in the standard of care group numerically, the difference did not reach statistical significance, although a trend towards significance was seen in one laboratory s analysis. An important secondary endpoint from the trial, change in plaque volume in the most severely diseased subsegment, showed statistically significant regression from baseline by an average of 4.8%. The results also demonstrated a significant reduction in myeloperoxidase, an inflammatory biomarker that correlates with future cardiovascular events. Overall adverse event rates were similar in the AGI-1067 and standard of care groups, and AGI-1067 was generally well tolerated.

Based on the results of an End of Phase II meeting with the U.S. Food and Drug Administration, or FDA, we proceeded to develop a pivotal Phase III clinical trial protocol to evaluate AGI-1067 for the treatment of atherosclerosis. The Phase III protocol received a Special Protocol Assessment from the FDA in March 2003. A Special Protocol Assessment is written confirmation from the FDA that the protocol is adequately designed to support a New Drug Application for the drug in the specified treatment area.

In 2003, we initiated the pivotal Phase III trial, referred to as ARISE (Aggressive Reduction of Inflammation Stops Events), which is being conducted in cardiac centers in the United States, Canada, the United Kingdom and South Africa. ARISE will evaluate the impact of AGI-1067 on important outcome measures such as death due to coronary disease, myocardial infarction, stroke, coronary re-vascularization and unstable angina in patients who have CHD. The study will assess the incremental benefits of AGI-1067 versus the current standard of care therapies in this patient

population. As such, all patients in the trial, including those on placebo, will be receiving other appropriate heart disease medications, including statins and other cholesterol-lowering therapies, high blood pressure medications and anti-clotting agents.

We originally planned to enroll in ARISE 4,000 patients who would be followed for an average of 18 months or until a minimum of 1,160 primary events, or outcome measures, had occurred. In February 2005, we announced that the FDA approved our proposed amendment to the ARISE Phase III clinical trial protocol. The changes to the ARISE protocol are intended to enhance the trial as well as to accelerate its pace without affecting the Special Protocol Assessment with the FDA. The changes approved by the FDA include our plan to increase the number of patients in the study to a target of 6,000, eliminate the minimum 12 month follow-up period for patients and decrease the minimum number of primary events to 990. With these modifications, we would expect to complete enrollment by mid-2005 and complete the ARISE trial by the end of the first quarter of 2006. We then plan to file a New Drug Application with the FDA as soon as possible after we complete the trial and analyze the results.

Table of Contents

AGI-1096

Organ transplant rejection is caused when patients immune systems recognize transplanted organs as foreign and, therefore, reject them. Acute rejection occurs soon after transplantation, while chronic rejection may take years. Recent industry sources report there are approximately 200,000 organ transplant recipients in the United States who are at risk of chronic organ transplant rejection. Chronic rejection is a major factor contributing to organ shortage.

Physicians treat these patients with powerful immunosuppressants to block all immune and inflammatory reactions that could cause organ transplant rejection. These immunosuppressive therapies, however, may place patients at increased risk for infection. The vascular protection provided by our drug candidate may protect organs from rejection beyond the first year without increasing the risk of infection.

Our second v-protectant® candidate, AGI-1096, is a novel antioxidant and selective anti-inflammatory agent which is being developed to address the accelerated inflammation of grafted blood vessels, known as transplant arteritis, common in chronic organ transplant rejection. AGI-1096 inhibits the expression of certain inflammatory proteins, including VCAM-1, in endothelial cells lining the inside surfaces of blood vessel walls. We have completed a Phase I clinical trial of AGI-1096 in healthy volunteers that demonstrated AGI-1096 was well-tolerated over the escalating single oral doses studied. Adverse events were generally mild and not considered clinically significant. Subjects reached targeted blood levels for AGI-1096 that were equivalent to those seen in successful preclinical models of organ transplant rejection. In January 2004, we announced a collaboration with Fujisawa Pharmaceutical Co., Ltd. to conduct preclinical and early-stage clinical trials, with Fujisawa funding all development costs during the term of the agreement. Fujisawa will also receive an option to negotiate for late stage development and commercial right to AGI-1096.

Other V-Protectant® Candidates

Rheumatoid arthritis is a chronic, progressively debilitating inflammatory disease that affects articular, or rotating, joints resulting in significant pain, stiffness and swelling and leads to degradation of the joint tissue. According to the Arthritis Foundation, there are 2.1 million people with rheumatoid arthritis in the United States. Approximately 70 percent of patients with rheumatoid arthritis are young and middle-aged women.

Physicians treat rheumatoid arthritis in a stepwise fashion, starting with the occasional to regular use of anti-inflammatory agents such as aspirin or ibuprofen, and proceeding to treatment with DMARDs, which can potentially be toxic. The newer DMARDs target the modulation of tumor necrosis factor (TNF), tissue repair and proliferation. The recent successful introduction of new drugs for rheumatoid arthritis has highlighted both the market potential and the size and scope of the unmet medical need of these patients. These drugs are partially effective and may cause serious side effects.

We previously were developing AGIX-4207, a v-protectant® candidate for the treatment of rheumatoid arthritis. In October 2003, we initiated the enrollment in a Phase II clinical trial called OSCAR, a multi-center, randomized, double-blind, placebo-controlled trial of approximately 275 patients. The patients were randomized into four groups and treated with one of three doses of AGI-4207 or placebo, administered orally, once a day, for 12 weeks. In October 2004, we announced the results of the OSCAR clinical trial, which evaluated the impact of various doses of AGIX-4207 versus placebo on clinical efficacy, biomarkers and safety in patients with rheumatoid arthritis. The results indicated that none of the three dosing arms of AGIX-4207 showed a statistically significant improvement in ACR 20 scores, a standard measurement of response utilized to evaluate improvement, when compared to placebo, the primary efficacy end point of the trial. Two of the pre-specified secondary endpoints, tender joint count and morning stiffness, did show statistically significant improvement when compared to placebo. Based on the aggregate findings of the study, however, we have discontinued clinical development of AGIX-4207 and the intravenous dosage form of

AGIX-4207. We continue to have an active program aimed at investigating other v-protectants® in rheumatoid arthritis and have identified other compounds with enhanced therapeutic potential within our rheumatoid arthritis preclinical models. We are working to select another candidate to move into formal preclinical development.

We have also identified additional potential v-protectant® candidates to treat other chronic inflammatory diseases, including asthma. According to the American Lung Association, approximately 20 million adults and children in the United States currently suffer from asthma. Current therapies that target the underlying disease include corticosteroids and several classes of drugs that relieve symptoms but are not effective for chronic inflammation. We believe that v-protectants® may reduce the inflammation associated with chronic asthma.

Table of Contents

We are evaluating these v-protectants® to determine lead drug candidates for clinical development. We plan to develop these v-protectants® rapidly and may seek regulatory fast track status, if available, to expedite development and commercialization. We will continue to expand upon our v-protectant® technology platform using functional genomics to identify novel therapeutic gene targets.

Discovery Research Program

We have built a robust Discovery Research Program using our demonstrated expertise in functional genomics, molecular biology, cell biology, physiology, pharmacology, biochemistry and medicinal chemistry.

Our Discovery Research Program has four main objectives:

To discover and develop v-protectants® with enhanced potency and improved therapeutic properties. We are synthesizing novel compounds and testing them in a variety of biochemical and cell-based assays to discover and develop new, small molecule v-protectants®. We believe that these v-protectants® will have improved therapeutic properties and applicability across a wide range of chronic inflammatory diseases. We have identified several novel series of highly potent v-protectants®.

To identify novel anti-inflammatory therapeutic targets utilizing functional genomics. One part of our drug discovery platform is a set of techniques that connects our knowledge of genes, which code for proteins, to agents that modify gene activity. This collection of methods, called functional genomics, enables us to select targets efficiently. Our targets for therapy may be the gene, the protein, another substance in the body that links to the protein, or the agent that induces the change. For example, oxidants are agents that induce changes in gene activity. We believe our functional genomics program will enable us to identify novel genes and their protein products that are critical to the chronic inflammatory disease process. We plan to progress these genes and proteins into targets for novel classes of drugs.

To develop new classes of v-protectant® drugs based on the new therapeutic targets identified by our functional genomics program. We are identifying enzymes and other molecular targets that either control or are controlled by oxidant signals. We believe these discoveries will enable our chemists to synthesize the next generation of v-protectants®. We intend to use these enzymes and other molecular targets for both internal efforts and as strategic collaboration assets.

To develop a second broad platform for the discovery and development of a new class of anti-inflammatory drug candidates. As a result of entering into the license agreement with National Jewish Medical and Research Center in June 2001, we have expanded our research program to include the discovery and development of new drug candidates through the exploitation of the licensed technology.

Patents and Intellectual Property

We have established a patent portfolio of owned and in-licensed patents that cover our lead compounds and their use. It is our goal to pursue both broad and specific patent protection in the key areas of our research and development both in the United States and internationally, and to identify value-added exclusive in-licensing opportunities.

V-Protectant® Technology

We have license agreements with Emory University and The Regents of the University of California covering aspects of our v-protectant® technology. These agreements obligate us to make milestone payments upon attainment of agreed-upon goals and royalty payments on the sale of licensed products and technology. The licenses with Emory University and The Regents of the University of California also require us to be diligent in commercializing the

licensed technologies within certain time periods.

Under our license agreement with Emory University, Emory University granted to us an exclusive license to make, use and sell methods and products covered by certain patents and patent applications owned by Emory University relating generally to the treatment and diagnosis of VCAM-1 related diseases. The license agreement requires us to make royalty payments to Emory University based on certain percentages of net revenue we derive from sales of products covered by the licensed patents or patent applications, and from sublicensing of the licensed patents or patent applications. The license agreement also requires us to make

Table of Contents

milestone payments to Emory University upon the occurrence of certain product development events. Milestone payments for AGI-1067 could total $250,000 if all milestone objectives are met. We must indemnify Emory University for all claims and/or losses caused or contributed to by AtheroGenics arising out of our use of the license. We have procured commercial general liability insurance in specified amounts customary in the industry naming Emory University as an insured.

The Emory license agreement will terminate when all patent rights licensed under the agreement expire. Emory University may terminate the agreement if, after Emory gives notice to us, we fail to make a payment, we fail to render progress reports, we incur specified financial problems, we decide to no longer develop licensed products under the agreement, or we breach a material term of the agreement. We may terminate the agreement upon advance notice to Emory, or if Emory University violates certain material terms of the agreement.

Under our license agreement with The Regents of the University of California, we received a license to make, use and sell diagnostic and therapeutic methods and products using monoclonal antibodies in atherosclerosis and other diseases, which are claimed in applicable patent applications owned by The Regents of the University of California in the U.S. and Canada. We must make milestone payments to The Regents of the University of California upon occurrence of various product development events of up to $45,000 for each therapeutic application and $35,000 for each diagnostic application. In addition, we must pay to The Regents of the University of California a percentage of the net revenue we receive from the sale of products covered by the patents and patent applications and from our sublicensing the licensed patents and patent applications. The Regents of the University of California may terminate the agreement upon proper notice for violation of material terms of the agreement. The agreement expires in 2018, when the last patent covered by the license expires. We may terminate the agreement at any time upon prior notice to The Regents of the University of California. We must indemnify The Regents of the University of California for all losses and claims arising out of our use of the license. In addition, we have procured commercial liability insurance in specified amounts customary in the industry naming the University of California as an insured.

As part of our v-protectant® technology patent portfolio, we also purchased U.S. Patent No. 5,262,439 under an agreement with Dr. Sampath Parthasarathy. We believe the cost of this agreement to us is immaterial.

AGI-1067 Patent Portfolio

Our patent coverage on AGI-1067 is based on patent filings that we own and patent filings exclusively licensed from Emory University. We own one issued patent, U.S. Patent No. 5,262,439, which expires in 2012, and related filings in Japan, Canada and Europe that generically cover the compound AGI-1067 as a member of a class of related compounds. We own another patent, U.S. Patent No. 6,147,250, that protects through 2018 the specific compound AGI-1067 and its use to treat VCAM-1 mediated diseases including, among others, atherosclerosis, post-angioplasty restenosis and coronary artery disease. We also own U.S. Patent No. 6,121,319, which covers the use of a class of compounds including AGI-1067 to treat VCAM-1 mediated diseases. Applications corresponding to U.S. Patent No. 6,147,250 and U.S. Patent No. 6,121,319 have also been filed in foreign patent offices. The patents that we have exclusively licensed from Emory University include the use of a substance that inhibits a class of oxidant signals to treat diseases mediated by VCAM-1.

AGI-1096 Patent Portfolio

Our patent coverage on AGI-1096 is based on patent filings that we own and patent filings exclusively licensed from Emory University. We own U.S. Patent No. 6,617,352 and associated non-U.S. patent filings which describe AGI-1096 and its use to treat disorders mediated by VCAM-1. We also own U.S. Patent No. 6,670,398 which claims method of using AGI-1096 for treating transplant organ rejection. These patents and any associated non-U.S. counterparts will expire in 2018.

AGIX-4207 Patent Portfolio

Our patent coverage on AGIX-4207 is based on patent filings that we own and patent filings exclusively licensed from Emory University. We own U.S. Patent No. 6,548,699, and associated non-U.S. patent filings which describe AGIX-4207 and its use to treat rheumatoid arthritis, other inflammatory conditions and other disorders mediated by VCAM-1. This patent and its associated non-U.S. counterparts will expire in 2018.

Table of Contents

Other V-Protectant® Compounds

Certain patent applications in the United States and non-U.S. countries cover the use of a number of compounds identified in our research program to act as v-protectants®, and specifically for use in treating cardiovascular and inflammatory disease. In addition we have exclusively licensed patents from Emory University that cover the use of a class of compounds which act as v-protectants®.

MEKK Technology

In June 2001, we entered into a worldwide exclusive license agreement with National Jewish Medical and Research Center. Under the agreement, National Jewish granted us an exclusive license under several of its U.S. and foreign patents and patent applications and related technical information to make, use and sell diagnostics and therapeutics for the treatment of human diseases, including inflammation and asthma. Under the terms of the agreement with National Jewish, we may grant sublicenses of our rights to others.

Under the agreement with National Jewish, we have assumed responsibility for all future costs associated with research and development of products developed from the licensed technology. We have also assumed responsibility for the costs of filing, prosecuting and maintaining the licensed patent rights. We granted National Jewish a warrant to purchase up to 40,000 shares of our common stock at an exercise price of $6.00 per share, subject to a vesting period. Under the agreement, we made an upfront payment in connection with the execution of the agreement and will pay milestone payments to National Jewish upon the achievement of certain clinical and regulatory milestones. Upfront and milestone payments could aggregate up to approximately $800,000. If we fail to meet various performance milestones by certain dates, some or all of the licensed technology will revert to National Jewish. We must also pay a royalty to National Jewish on net sales of licensed products. If we sublicense the licensed technology, we must pay to National Jewish a percentage of the amounts paid to us by the sublicensee.

We may terminate the license agreement with National Jewish at any time upon at least 90 days prior written notice. If we terminate the agreement in this manner, all licensed patent rights and related technology revert to National Jewish. Either party to the agreement may also terminate it upon a material, uncured breach by the other, or upon the bankruptcy or insolvency of the other. We must indemnify National Jewish for all losses and claims arising out of our use of the license. We will procure commercial liability insurance in amounts customary in the industry as required by the agreement.

Our patent position, like that of many pharmaceutical companies, is uncertain and involves complex legal and factual questions for which important legal principles are unresolved or unclear. We may not develop or obtain rights to products or processes that are patentable. Even if we do obtain patents, they may not adequately protect the technology we own or in-license. In addition, others may challenge, seek to invalidate, infringe or circumvent any patents we own or in-license, and rights we receive under those patents may not provide competitive advantages to us.

Our commercial success will depend in part on our ability to manufacture, use, sell and offer to sell our product candidates and proposed product candidates without infringing patents or other proprietary rights of others. We may not be aware of all patents or patent applications that may impact our ability to make, use or sell any of our product candidates or proposed product candidates. For example, U.S. patent applications do not publish until 18 months from their effective filing date. Further, we may not be aware of published or granted conflicting patent rights. Any conflicts resulting from patent applications and patents of others could significantly reduce the coverage of our patents and limit our ability to obtain meaningful patent protection. If others obtain patents with conflicting claims, we may be required to obtain licenses to these patents or to develop or obtain alternative technology. We may not be able to obtain any licenses or other rights to patents, technology or know-how necessary to conduct our business as described in this report. Any failure to obtain such licenses or other rights could delay or prevent us from developing or

commercializing our product candidates and proposed product candidates, which could materially affect our business.

Litigation or patent interference proceedings may be necessary to enforce any of our patents or other proprietary rights, or to determine the scope and validity or enforceability of the proprietary rights of others. The defense and prosecution of patent and intellectual property claims are both costly and time consuming, even if the outcome is favorable to us. Any adverse outcome could subject us to significant liabilities, require us to license disputed rights from others, or require us to cease selling our future products.

Table of Contents

Trademarks

The U.S. Patent and Trademark Office issued a Certificate of Registration for the trademark OXYKINE on April 10, 2001. The Patent and Trademark Office issued a Certificate of Registration for the trademark AATHEROGENICS and design on November 7, 2000 and issued one for the trademark AGI on September 19, 2000. On February 3, 2003, we applied for the trademark V-PROTECTANT.

On January 30, 2002, Applied Genetics Incorporated Dermatics filed with the United States Patent and Trademark Office a petition to cancel the trademark AGI. Applied Genetics has not requested any monetary damages. We filed an answer to the petition on March 11, 2002. On July 12, 2002, the United States Patent and Trademark Office issued a suspension of the cancellation proceeding to allow the parties to negotiate a settlement. A settlement agreement has been reached between both parties and is pending approval with the Patent Office.

Manufacturing

We have entered into arrangements with third party manufacturers for the supply of AGI-1067 bulk drug substance and for the formulated drug product for use in our ongoing and currently planned clinical trials. The suppliers of the bulk drug substance for AGI-1067 operate under current Good Manufacturing Practice guidelines using cost-effective and readily available materials and reliable processes. The starting material used in the manufacturing process of AGI-1067 is Probucol USP, a material that is available from a number of suppliers worldwide. We have sufficient quantities to support development activities for the foreseeable future. Another third party supplier formulates AGI-1067 into the drug product under current Good Manufacturing Practice guidelines. We anticipate that these suppliers will be able to provide sufficient formulated drug product to complete our ongoing and currently planned clinical trials.

We plan to establish manufacturing agreements with third parties that comply with Good Manufacturing Practice guidelines for bulk drug substance and oral or intravenous formulations of our v-protectant® product candidates to support both ongoing and planned clinical trials as well as commercial marketing of the products following regulatory approval.

Sales and Marketing

We plan to collaborate with large pharmaceutical companies to commercialize product candidates that are for patient or physician populations in broad markets. We believe that collaborating with large companies that have significant marketing and sales capabilities provides for optimal penetration into broad markets, particularly those areas that are highly competitive. In contrast, we plan to develop a sales force to commercialize the products targeted at appropriate patient and physician populations in narrow markets. By using our own sales and marketing organization, we believe we can retain a higher percentage of the profits generated from the sale of our products.

Competition

Developments by others may render our product candidates obsolete or noncompetitive. We face intense competition from other companies for collaborative arrangements with pharmaceutical, biotechnology and medical device companies for establishing relationships with academic and research institutes and for licenses to proprietary technology. These competitors, either alone or in collaboration, may succeed in developing technologies or products that are more effective than ours.

We believe pharmaceutical, biotechnology and medical device companies, as well as academic and research institutions and government agencies, have drug discovery and development programs related to our named

therapeutic areas of interest. Many of these companies and institutions, including, but not limited to, Pfizer Inc., GlaxoSmithKline, Johnson & Johnson and Novartis AG, have targeted indications that overlap significantly with our targets and have substantially greater resources than we do. They may, therefore, succeed in commercializing products before we do that compete with us on the basis of efficacy, safety and price.

Our ability to compete is predicated on three related factors:

First, our scientists and their collaborators have pioneered the basic discoveries and research methodologies linking oxidant signals to vascular cell inflammation. These discoveries and research methodologies form the foundation for our proprietary drug discovery programs relating to chronic inflammation.

Table of Contents

Second, our scientific expertise, coupled with our expertise in clinical drug development, has enabled us to be the first company to conduct clinical trials of an orally-administered, small molecule v-protectant®.

Third, we believe our scientific, development and licensing expertise strongly positions us to acquire promising technologies and products discovered outside AtheroGenics.

Governmental Regulation

We plan to develop prescription-only drugs for the foreseeable future. The U.S. Food and Drug Administration is the regulatory agency that is charged with the protection of people in the United States who take prescription medicines. Every country has a regulatory body with a similar mandate. In addition, the European Union has vested centralized authority in the European Medicines Evaluation Agency and Committee on Proprietary Medicinal Products to standardize review and approval across member nations.

Regulatory agencies have established guidelines and regulations for the drug development process. This process involves several steps. First, the drug company must generate sufficient preclinical data to support initial human testing. In the United States, the drug company must submit an Investigational New Drug application prior to human testing. The Investigational New Drug application contains adequate data on product candidate chemistry, toxicology and metabolism and, where appropriate, animal research testing to support initial safety evaluation in humans. In addition, the drug company provides to the FDA a clinical plan, including proposed use and testing in subjects comprising healthy volunteers and patients.

Clinical trials for a new product candidate usually proceed through four phases:

Phase I clinical trials explore safety, blood levels, metabolism and the potential for interaction with other drugs. Phase I typically proceeds from healthy volunteers into patients with the target disease and comprises up to approximately 200 total subjects.

Phase II clinical trials establish a dose for future testing and marketing in an adequate number of patients with the target disease. The clinical trials may include hundreds of patients who have the target disease and who are receiving a range of background medications. In addition, Phase II clinical trials verify the mechanisms of action proposed preclinically.

Phase III clinical trials usually include two adequate and well controlled studies in the target population. For most chronic diseases, drug companies study a few thousand patients to assure a broadly applicable assessment of safety and efficacy.

At the successful conclusion of Phase III, drug companies may submit a product license application, called a New Drug Application in the United States. Upon accepting the submission, the FDA or non-U.S. regulatory authorities review the file for completeness, accuracy and adherence to regulations. These authorities may use internal and external consultants and may convene an expert committee to advise on the safety, effectiveness and usefulness of the proposed new product candidate prior to final regulatory judgment. The final step to registration is approval of the package insert or label that defines what the drug company may promote to physicians who may use the new drug.

Phase IV clinical trials provide additional information to support marketing of the drug for its approved indication. Phase IV clinical trials may generate data to support promotion of the new drug in comparison with other approved drugs and to support healthcare economics claims. In addition, every pharmaceutical company is responsible for post-marketing surveillance for safety in the marketplace.

We must meet regulatory standards prior to exposing subjects to any drug candidate. We remain responsible for any of these development activities whether we perform them internally or contract them to a third party. The FDA may audit us or our third party contractors at any time to ascertain compliance with standards. The FDA may halt all ongoing work if it determines that we or our contractors have deviated significantly from these standards. These standards include:

Good Manufacturing Practices, which govern process chemistry, formulation, labeling and handling of a drug throughout its life cycle;

Table of Contents

Good Laboratory Practices, which govern the use of a drug in animal studies to support establishment of safety or the disposition and metabolism of the administered drug, and handling of human or other biological samples for drug assays; and

Good Clinical Practices, which govern the exposure of human subjects under our protocols. Good Clinical Practices set standards for the constitution and activities of institutional review boards that are charged with assuring that the appropriate person gives informed consent prior to study participation and protecting patients whether they receive an experimental drug, an approved drug, or an inactive look-alike called a placebo.

In addition, our research and development processes and manufacturing activities involve the controlled use of hazardous materials, chemicals and radioactive materials and produce waste products. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposing of hazardous materials and waste products.

Advertising is subject to FDA approval in the United States and national review elsewhere. In addition, state and local governments and other federal agencies may control marketing if the drug substance, formulation, package, intended use or disposal is subject to local regulation.

The FDA has expanded its expedited review process in recognition that certain severe or life-threatening diseases and disorders have only limited treatment options. Fast track designation expedites the development process but places greater responsibility on a drug company during Phase IV clinical trials. The drug company may request fast track designation for one or more indications at any time during the Investigational New Drug application process, and the FDA must respond within 60 days. Fast track designation allows the drug company to develop product candidates faster based on the ability to request an accelerated approval of the New Drug Application (NDA). For accelerated approval the clinical effectiveness is based on a surrogate endpoint in a smaller number of patients. In addition, the drug company may request priority review at the time of the NDA submission. If the FDA accepts the NDA submission as a priority review, the time for review is reduced from one year to six months. We plan to request fast track designation and/or priority review, as appropriate, for internal drug development programs.

Research and Development

Our research and development expenses in 2004, 2003 and 2002 were $59.2 million, $46.7 million and $23.7 million, respectively. We plan to increase significantly our research and development expenses as we continue to invest in our clinical programs.

Employees

We currently have 106 full-time employees, including 85 in research and development. The employee group includes 29 employees with Ph.D.s, six with M.D.s and 23 with Masters degrees. We believe that our employee relations are good.

Available Information

Our internet website is located at www.atherogenics.com. Copies of our reports filed under Section 13(a) or 15(d) of the Exchange Act, including annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and all amendments to these reports, may be accessed from our website, free of charge, as soon as reasonably practicable after these reports are electronically filed with or furnished to the Securities and Exchange Commission. The reference to our website address does not constitute incorporation by reference of the information contained on the website, which should not be considered part of this document.

12

Table of Contents

Scientific Advisory Board

We have established a scientific advisory board to provide guidance and counsel on aspects of our business. The board convenes once a year and individual members are contacted as required. Members of the board provide input on product research and development strategy, education and publication plans. The names and members of the board are as follows:

R. Wayne Alexander, M.D., Ph.D., *Chairman*	Chairman, Department of Medicine, Emory University School of Medicine
William W. Busse, M.D.	Professor of Medicine, Director, Allergy and Clinical Immunology Department, University of Wisconsin Medical School
Victor J. Dzau, M.D.	Chancellor, Health Affairs, Duke University Medical Center
Erwin W. Gelfand, M.D.	Chairman, Department of Pediatrics, National Jewish Medical and Research Center
David G. Harrison, M.D.	Professor of Medicine, Director, Division of Cardiology, Emory University School of Medicine
Gary L. Johnson, Ph.D.	Professor and Chairman, Department of Pharmacology, University of North Carolina School of Medicine
Peter Libby, M.D.	Mallinckrodt Professor of Medicine, Harvard Medical School, Chief, Cardiovascular Division Department of Medicine, Brigham and Women s Hospital
David M. Stern, M.D.	Dean, School of Medicine, Chief Clinical Officer, Cardiovascular Division Department of Medicine, Brigham and Women s Hospital

Forward-Looking Statements and Risks Related to Our Company and Business

The Private Securities Litigation Reform Act of 1995 provides a safe harbor for forward-looking statements made by or on behalf of AtheroGenics. AtheroGenics and its representatives may from time to time make written or oral forward-looking statements, including statements contained in this report and our other filings with the Securities and Exchange Commission and in our reports to our shareholders. Generally, the words, believe, expect, intend, estimate anticipate, will and similar expressions identify forward-looking statements. All statements which address operating performance, events or developments that we expect or anticipate will occur in the future, including projections of our future results of operations or of our financial condition, research, development and commercialization of our product candidates, and anticipated trends in our business, are forward-looking statements within the meaning of the Reform Act. The forward-looking statements are and will be based on our then current views and assumptions regarding future events and operating performance, and speak only as of their dates. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

The following are some of the factors that could affect our financial performance or could cause actual results to differ materially from those expressed or implied in our forward-looking statements:

Risks Related to Our Financial Results and Need for Additional Financing

We have a history of operating losses, and we may not generate revenue or achieve profitability in the future.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with collaborators, to complete successfully the development of our product candidates, conduct preclinical tests in animals and clinical trials in human beings, obtain the necessary regulatory approvals and manufacture and market the resulting drugs. We have had no significant revenue to date. We have experienced operating losses since we began operations in 1994. As of December 31, 2004, we had an accumulated deficit of approximately $212.1 million. We expect to incur additional operating losses and expect cumulative losses to increase substantially as

Table of Contents

our research and development, preclinical, clinical, manufacturing and marketing efforts expand. If we are unable to achieve and then maintain profitability, the market value of our common stock and our outstanding notes will decline.

If we need additional financing and cannot obtain it, we may not be able to develop or market our products.

We expect our research and development expenses to increase in connection with our ongoing activities, particularly in connection with the ARISE trial that we initiated in June 2003. We believe that our existing cash, cash equivalents and short-term investments will be sufficient to enable us to fund our operating expenses, obligations under our financing arrangements and capital expenditure requirements for at least the next 12 months. Our future capital requirements will depend on many factors, including:

- the scope and results of our research, preclinical and clinical development activities;
- the timing of, and the costs involved in, obtaining regulatory approvals;
- our ability to establish and maintain collaborations and the financial terms of any collaborations;
- the cost of commercialization activities, including product marketing, sales and distribution;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims and other patent-related costs;
- the costs related to purported class action lawsuits filed against us, as described under Item 3. Legal Proceedings ; and
- the extent to which we acquire or invest in businesses, products and technologies.

If our future capital requirements exceed our available funds, we will need to seek additional financing. We may be unable to raise capital when needed or on attractive terms. If additional funds are not available, we may need to delay clinical studies, curtail operations or obtain funds through collaborative arrangements that may require us to relinquish rights to some of our products or potential markets.

Risks Related to Development of Product Candidates

We depend heavily on the success of our most advanced internal product candidate, AGI-1067 for atherosclerosis, which is in clinical development. If we are unable to commercialize this product candidate, or experience significant delays in doing so, our business will be materially harmed.

AGI-1067 is our lead compound. Our ability to generate product revenues will depend heavily on the successful development and commercialization of this compound. The commercial success of AGI-1067 will depend on several factors, including the following:

- successful completion of clinical trials;
- receipt of marketing approvals from the FDA and similar foreign regulatory authorities;
- establishing commercial manufacturing arrangements with third party manufacturers;
- launching commercial sales of the product, either alone or in collaboration with others; and

acceptance of the product in the medical community and with third party payors.

AGI-1067 could fail in clinical trials if we are unable to show it is effective or if it causes unacceptable side effects in the patients we treated. While the plaque regression observed in the group treated with AGI-1067 in the CART-2 trial exceeded that observed in the standard of care group numerically, the difference was not statistically significant. Moreover, the results of our Phase II clinical trials of AGI-1067 are not necessarily indicative of the results we will obtain in our Phase III clinical trial of AGI-1067, particularly because

Table of Contents

the primary clinical endpoints of these trials are not the same. Failure in clinical trials of AGI-1067 would have a material adverse effect on our ability to generate revenue or become profitable. If we are not successful in commercializing AGI-1067, or are significantly delayed in doing so, our business will be materially harmed.

If we do not successfully develop our other product candidates, we will have limited ability to generate revenue.

Other than AGI-1067, all of our other product candidates are in early stages of development, and only one other product candidate has undergone Phase I clinical trials. Our product candidates are subject to the risks of failure inherent in developing drug products based on new technologies. We do not expect any of our potential product candidates, including AGI-1067, to be commercially available until at least 2007. Our drug discovery efforts may not produce any other proprietary product candidates. Our failure to develop product candidates will limit our ability to generate additional revenue.

If we fail to demonstrate adequately the safety and efficacy of a product candidate, we will not be able to commercialize that product candidate.

Product candidates we develop, alone or with others, may not prove safe and effective in clinical trials and may not meet all of the applicable regulatory requirements needed to receive regulatory approval. If we fail to adequately demonstrate safety and efficacy for any product candidate, we will not be able to commercialize that product candidate. Our failure to commercialize a product candidate will materially adversely affect our revenue opportunities. We will need to conduct significant research, preclinical testing and clinical trials before we can file product approval applications with the FDA and similar regulatory authorities in other countries. Preclinical testing and clinical trials are long, expensive and uncertain processes. We may spend several years completing our testing for any particular product candidate. Failure can occur at any stage. For example, we recently discontinued clinical development of AGI-4207 in rheumatoid arthritis following announcement of unsuccessful results of a Phase II clinical trial of that product candidate.

The FDA or we may suspend our clinical trials at any time if either of us believes that we are exposing the subjects participating in these trials to unacceptable health risks. The FDA or institutional review boards at the medical institutions and healthcare facilities where we sponsor clinical trials may suspend any trial indefinitely if they find deficiencies in the conduct of these trials. The FDA and these institutional review boards have authority to oversee our clinical trials, and the FDA may require large numbers of test subjects. In addition, we must manufacture the product candidates that we use in our clinical trials under the FDA s Good Manufacturing Practices.

Even if we achieve positive results in early clinical trials, these results do not necessarily predict final results. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials, even after achieving positive results in earlier trials. Negative or inconclusive results or adverse medical events during a clinical trial could cause the FDA or us to terminate a clinical trial or require that we repeat it.

In addition, even if we receive approval for commercial sale of any of our product candidates, after use in an increasing number of patients, our products could show side effect profiles that limit their usefulness or require their withdrawal although the drugs did not show the side effect profile in Phase I through Phase III clinical trials.

Risks Related to Our Dependence on Third Parties for Manufacturing, Research and Development and Marketing and Distribution Activities

We may not be successful in establishing collaborations for AGI-1067 and any other product candidate we may seek to commercialize, which could adversely affect our ability to discover, develop and commercialize products.

A key element of our business strategy is to collaborate with third parties, particularly leading pharmaceutical companies, to develop and commercialize some of our product candidates, including AGI-1067. We are currently seeking a collaborator for development and commercialization of AGI-1067. We also expect to seek collaborations for the development and commercialization of other product candidates in the future. The timing and terms of any collaboration for AGI-1067 will depend on the evaluation by prospective collaborators of the clinical trial results of AGI-1067 and other aspects of the drug s safety and efficacy profile. We are currently reviewing the results of our CART-2 trial of AGI-1067 with potential collaborators and cannot now predict the timing and terms of such a collaboration. If we are unable to reach agreements with suitable collaborators for AGI-1067 or any other product

Table of Contents

candidate, we would be forced to fund the entire development and commercialization of such product candidates, and we may not have the resources to do so. If resource constraints require us to enter into a collaboration early in the development of a product candidate, we may be forced to accept a more limited share of any revenues such products may eventually generate. We face significant competition in seeking appropriate collaborators. Moreover, these collaboration arrangements are complex and time-consuming to negotiate and document. We may not be successful in our efforts to establish collaborations or other alternative arrangements for AGI-1067 or any other product candidate.

We expect to depend significantly on collaborations with third parties to develop and commercialize some of our product candidates. If a potential collaborator were to change its strategy or the focus of its development and commercialization efforts with respect to our relationship, the success of our product candidates and our operations could be adversely affected.

Our collaboration with Fujisawa Pharmaceutical to develop AGI-1096 in preclinical testing and early-stage clinical trials and any other collaboration that we may establish may not be successful. The success of any collaboration arrangement will depend heavily on the efforts and activities of our collaborators. Collaborators will likely have significant discretion in determining the efforts and resources that they will apply to these collaborations. The risks that we anticipate being subject to in collaborations include:

a collaborator may develop and commercialize, either alone or with others, products and services that are similar to or competitive with the products that are the subject of the collaboration with us;

a collaborator may change the focus of its development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities from time to time, including following mergers and consolidations, which have been common in recent years in these industries;

the ability of our product candidates and products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products;

a collaborator may terminate a collaboration in the event of a material breach by us; and

a collaborator may fail to maintain or defend our intellectual property rights.

The termination of any collaboration that we may establish might adversely affect the development of the related product candidat