ALTEON INC /DE
Form 10-K
March 15, 2005

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

FORM 10-K

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2004, OR

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

FOR THE TRANSITION PERIOD FROM _____TO_____

Commission file number 001-16043

ALTEON INC.
(Exact name of Registrant as specified in its charter)

DELAWARE	13-3304550
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

6 CAMPUS DRIVE, PARSIPPANY, NEW JERSEY 07054
(Address of principal executive offices)
(Zip Code)

(201)934-5000
(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange On Which Registered
Common Stock, Par Value $.01 per share	American Stock Exchange

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

NONE

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, as amended, 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. [X]

Indicate by check mark whether the Registrant is an accelerated filer (as defined by Rule 12b-2 of the Act). Yes [X] No [ ]

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the American Stock Exchange closing price of the common stock ($1.18 per share), as of June 30, 2004, was $47,636,963.

At March 1, 2005, 57,996,711 shares of the Registrant's common stock, par value $.01 per share, were outstanding.

Documents Incorporated By Reference

The following documents (or parts thereof) are incorporated by reference into the following parts of this form 10-K: certain information required in Part III of this Annual Report on Form 10-K is incorporated from the Registrant's Proxy Statement for the Annual Meeting of Stockholders to be held on June 29, 2005.

PART I

ITEM 1. BUSINESS.

OVERVIEW

We are a product-based biopharmaceutical company engaged in the discovery and development of small molecule drugs to reverse or slow down diseases of aging and complications of diabetes. We have identified several promising product candidates that represent novel approaches to some of the largest pharmaceutical markets. Our lead compound, alagebrium chloride (formerly ALT-711), is in Phase 2 clinical development for systolic hypertension, diastolic dysfunction in heart failure, or DHF, and erectile dysfunction, or ED. As we announced in February 2005, and as discussed further below, we have voluntarily and temporarily suspended enrollment of patients into our ongoing clinical studies of alagebrium, pending receipt of additional pre-clinical data, which are expected by mid-year 2005. Prior to resuming enrollment in any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our Data Monitoring Committee, or DMC, Investigational Review Boards, or IRBs, and the U.S. Food and Drug Administration, or the FDA.

Our pharmaceutical candidates were developed as a result of our research on the Advanced Glycation End-Product, or A.G.E., pathway, a fundamental pathological process and inevitable consequence of aging that causes or contributes to many medical disorders. A.G.E.s are glucose/protein complexes that form as a result of circulating blood glucose molecules reacting with proteins throughout the body, and subsequently interacting and bonding (crosslinking) with other proteins. These pathological complexes affect the structural chemistry of blood vessels, tissues and organs throughout the body, resulting in increased stiffness and fibrosis, as well as impaired flexibility and compromised function. In addition, A.G.E.s have been shown to contribute to disease by adversely altering multiple inflammatory and metabolic pathways. A.G.E. accumulation and protein crosslinking occur slowly as the body ages and at an accelerated rate in diabetic patients because of high glucose levels. Cardiovascular diseases, such as systolic hypertension and DHF, as well as diabetic complications, such as nephropathy and ED, are among the many conditions that are pathological consequences of A.G.E. formation and crosslinking. There are no known positive attributes of A.G.E.s.

Our research and drug development activities targeting the A.G.E. pathway have taken three directions: the breaking of A.G.E. crosslinks between proteins in order to reverse damage, or A.G.E. Crosslink Breakers; the prevention or inhibition of A.G.E. formation, or A.G.E.-Formation Inhibitors; and the reduction of the A.G.E. burden through a novel class of anti-hyperglycemic agents, Glucose Lowering Agents, or GLA. We believe that we were the first company to focus on the development of compounds to treat diseases caused by A.G.E. formation and crosslinking. Since our inception, we have created an extensive library of novel compounds targeting the A.G.E. pathway and have actively pursued patent protection for these discoveries.

The primary focus of our current research and development activities is alagebrium, which is our lead product candidate, and we believe it to be the only A.G.E. Crosslink Breaker in advanced human clinical testing. Alagebrium is the first rapidly-acting oral agent designed to "break" A.G.E. crosslinks, the benefit of which may be to restore structure and function to blood vessels, tissues and organs, thereby reversing the damage caused by aging and diabetes.

In December 2004, we announced that findings of a two-year toxicity study indicated that male Sprague Dawley rats exposed to high doses of alagebrium over their natural lifetime developed dose-related increases in liver cell alterations and tumors, and that the liver tumor rate was slightly over the expected background rate in this gender and species of rat. The relevance of these findings to humans is unknown. Our DMC has reviewed the cumulative human safety data and previous pre-clinical experience of alagebrium and found that the data did not demonstrate an association with the lifetime carcinogenicity study in rats. We have previously completed four genotoxicity studies of alagebrium to help determine potential toxicities in humans, and these studies have not indicated any potential human risk. Earlier pre-clinical toxicity studies found no mutagenic or carcinogenic activity in either rats or mice. We also announced in December 2004 our intent to conduct a series of pre-clinical experiments to explore the mechanism by which the liver tumors developed and the relevance of such tumors to human exposure. In February 2005, based on initial findings from one of these subsequent studies that provided direction for further analysis, we voluntarily and temporarily suspended enrollment of new patients into our ongoing clinical studies pending receipt of additional pre-clinical data, which are expected by mid-year 2005. We expect that decisions regarding resumption of enrollment will be made at that time. Prior to resuming

enrollment in any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA.

Four clinical studies of alagebrium are ongoing. Of the approximately 1,300 patients who have participated in the Phase 1 and Phase 2 clinical studies of alagebrium to date, approximately 1,000 patients have received alagebrium and approximately 300 patients have received placebo. The compound has demonstrated an excellent safety profile in all human clinical testing to date.

We are actively developing alagebrium for the treatment of systolic hypertension, DHF and ED. In March 2004, we initiated a double-blind, placebo-controlled Phase 2b clinical trial of alagebrium in systolic hypertension, SPECTRA (Systolic Pressure EfficaCy and Safety TRial of Alagebrium). SPECTRA is designed to lower systolic blood pressure in patients with a systolic blood pressure reading of greater than or equal to 145 mm Hg by ambulatory blood pressure measurements, or ABPM, building upon positive data from previous Phase 2 studies, including a Phase 2a study in cardiovascular compliance and the Phase 2b SAPPHIRE/SILVER (Systolic And Pulse Pressure Hemodynamic Improvement by Restoring Elasticity/Systolic Hypertension

Interaction with Left VEntricular Remodeling) trial. SAPPHIRE/SILVER demonstrated the ability of alagebrium to significantly lower systolic blood pressure (when measured by ABPM) in patients with baseline systolic pressures of 140 mm Hg whose condition was uncontrolled despite treatment with one or more currently available blood pressure medications. As discussed above, in February 2005, we voluntarily and temporarily suspended enrollment of new patients into SPECTRA pending receipt of additional pre-clinical data. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment in SPECTRA, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA. We cannot predict at this time when enrollment in our clinical studies will resume, if ever. If we are unable to resume enrollment in our clinical studies in a timely manner, or at all, our business will be materially adversely affected.

In April 2004, we initiated PEDESTAL (Patients with Impaired Ejection Fraction and Diastolic Dysfunction: Efficacy and Safety Trial of ALagebrium), an open-label, Phase 2a study designed to continue the evaluation of alagebrium on diastolic dysfunction and left ventricular mass in patients with diastolic and systolic heart failure. In the previously-conducted Phase 2a DIAMOND (Distensibility Improvement And ReMOdeliNg in Diastolic Heart Failure) study, treatment with alagebrium over 16 weeks demonstrated a statistically significant reduction in left ventricular mass and a marked improvement in the initial phase of left ventricular diastolic filling. The study also showed statistically significant improvements in multiple quality of life measurements. In December 2004, we disclosed that preliminary data from PEDESTAL indicate trends consistent with positive data from DIAMOND. As with SPECTRA, in February 2005, we voluntarily and temporarily suspended enrollment of new patients into PEDESTAL pending receipt of additional pre-clinical data. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment in PEDESTAL, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA. We cannot predict at this time when enrollment in our clinical studies will resume, if ever. If we are unable to resume enrollment in our clinical studies in a timely manner, or at all, our business will be materially adversely affected.

In January 2004, we initiated a Phase 2a academic study of alagebrium in endothelial function. That study is being conducted at Johns Hopkins University School of Medicine, or JHU, under grants from the National Heart, Lung and Blood Institute and the Society of Geriatric Cardiology. In December 2004, we disclosed that these data are showing strong trends in key measures relating to improvements in carotid and brachial artery stiffness based on a series of advanced non-invasive measurements. An initial group of patients has completed the study, and data are expected to be presented in the first half of 2005. In February 2005, we voluntarily and temporarily suspended enrollment of new patients into the JHU study pending receipt of additional pre-clinical data. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment in any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA. We cannot predict at this time when enrollment in our clinical studies will resume, if ever. If we are unable to resume enrollment in our clinical studies in a timely manner, or at all, our business will be materially adversely affected.

In January 2005, we announced the initiation of a Phase 2a study of alagebrium in ED. EMERALD (Efficacy and Safety of Alagebrium in Erectile Dysfunction in Male Diabetics) will assess the ability of alagebrium

to restore erectile function in diabetic patients with moderate to severe ED who are insufficiently responsive to current treatment with Phosphodiesterase Type 5, or PDE5 inhibitors, the first class of orally-active compounds marketed for ED. In a pre-clinical rat model of diabetes, alagebrium has demonstrated the ability to restore erectile function through a unique mechanism of action. We have voluntarily and temporarily suspended enrollment of new patients into EMERALD pending receipt of additional pre-clinical data. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment in EMERALD, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA. We cannot predict at this time when enrollment in our clinical studies will resume, if ever. If we are unable to resume enrollment in our clinical studies in a timely manner, or at all, our business will be materially adversely affected.

For a detailed description of Current Clinical Studies, see page 7 and for Completed Clinical Studies, see page 9.

We continue to evaluate potential pre-clinical and clinical studies in other therapeutic indications in which A.G.E. Crosslink Breaker compounds may address significant unmet needs. In addition to our ongoing clinical studies in systolic hypertension, heart failure and ED, we have early research studies focused on atherosclerosis; Alzheimer's disease; photoaging of the skin; eye diseases, including Age-related Macular Degeneration, or AMD, and glaucoma; and diabetic complications, including renal diseases.

We were incorporated in Delaware in October 1986. In January 2004, we moved our headquarters to 6 Campus Drive, Parsippany, New Jersey 07054. Our web address is www.alteon.com and our telephone number is (201) 934-5000. We make available free of charge, through the "Investor Relations" section of our website, our annual reports on Form 10-K, our quarterly reports on Form 10-Q, our current reports on Form 8-K and all amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC.

In addition, the public may read and copy materials we file with the SEC at the SEC's Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. The SEC Internet address is www.sec.gov.

See our financial statements for financial information required under this Item.

OUR BUSINESS STRATEGY

Our strategy is to develop drug candidates from our proprietary portfolio of new chemical entities. These compounds address large medical needs that are unmet by existing therapies. We will seek, as appropriate, to selectively out-license or co-develop our drug candidates with corporate partners. As we continue the clinical development of alagebrium, we may elect to retain development and marketing rights for one or several indications in North America, while at the same time continuing to evaluate potential corporate partnerships for the further development and ultimate marketing of the compound. In addition to alagebrium, we have identified compounds in multiple chemical classes of A.G.E. Crosslink Breakers and A.G.E.-Formation Inhibitors that may warrant further evaluation and potential development.

MARKETS OF OPPORTUNITY

Our research and development efforts have led us to an initial focus on cardiovascular and other vascular diseases, including hypertension, heart failure and ED, as well as other complications of diabetes. Therapeutic targeting of the A.G.E. pathway may reverse the progressive fibrosis and stiffening of blood vessels, tissues and organs, as well as diminish deleterious inflammatory and metabolic responses caused by A.G.E.s, thus potentially broadening our markets of opportunity to include additional medical disorders related to aging and diabetes. Importantly, there are no currently marketed drugs of which we are aware that are known to work directly on A.G.E.s and the structural stiffening of blood vessels and organs that lead to diseases such as systolic hypertension, heart failure and ED.

Cardiovascular Diseases

According to the American Heart Association, more than 64 million Americans have one or more types of heart or blood vessel disease, with 50 million Americans estimated to have high blood pressure. The latest World Health Organization - International Society of Hypertension guidelines for the management of hypertension emphasize the importance of pulse pressure (the difference between systolic and diastolic pressures) and arterial stiffness as predictors of overall cardiovascular risk. Currently available anti-hypertensive agents, which address a multi-billion dollar market, commonly reduce pressure on the vessel wall in such a manner as to lower both systolic and diastolic blood pressures and may not significantly affect pulse pressure. Published studies have shown that a 10 mm Hg reduction in pulse pressure correlates with approximately a 35% reduction in cardiovascular mortality.

Systolic Hypertension

Systolic hypertension, defined as elevated systolic blood pressure greater than 140 mm Hg, is the most common form of hypertension in those over the age of 50, with an estimated prevalence of nearly 25 million Americans. It is associated with a significantly increased risk of overall mortality, cardiovascular mortality and congestive heart failure. According to the American Heart Association, it is the type of hypertension least likely to be well treated. The potential ability of alagebrium to decrease pulse pressure and increase large artery compliance offers an opportunity to provide a treatment option specifically for systolic hypertension. See "--A.G.E. Crosslink Breakers - Alagebrium." Although currently marketed anti-hypertensive agents are being used to treat the disease, it is not adequately treated by these therapies. We believe that alagebrium may provide additional benefit because it exerts its activity by directly targeting the stiff vessels that are associated with systolic hypertension, a mechanism of action different from currently marketed anti-hypertension drugs. In addition, based on clinical trial results to date, it appears to be well tolerated in patients with hypertension.

Diastolic Dysfunction in Heart Failure/Left Ventricular Hypertrophy

Diastolic dysfunction is the impaired ability of the heart to relax and fill properly after a contraction, in part due to the stiffening of the heart tissue. It is characterized by higher than normal pressures during the relaxing phase of the heart cycle (diastole). If the heart tissue (interstitium) has become stiffened, the filling of the heart will be impaired. When the ventricles (the heart's lower pumping chambers) do not relax and fill normally, increased pressure and fluid in the blood vessels of the lungs may be a result (pulmonary congestion), resulting in shortness of breath. Diastolic dysfunction can also cause increased pressure and fluid in the blood vessels returning to the heart

(systemic congestion). Diastolic dysfunction is common to both systolic and diastolic heart failure in a group that collectively numbers about five million in the United States alone. DHF, which is estimated to account for 30% to 50% of all heart failure cases, is an especially poorly treated medical condition. We believe that alagebrium may offer promise as a novel therapy for cardiovascular diseases related to diastolic dysfunction because currently available therapies do not specifically target the stiffening of the heart and vessel walls.

Left ventricular hypertrophy, or LVH, refers to the thickening of the left ventricle that can occur progressively with hypertension. It can lead to decreased cardiac output, the inability to meet the circulatory needs of the body and to heart failure itself. It is a condition associated with many cardiovascular diseases, including systolic hypertension and DHF. In the DIAMOND study, patients who were treated with alagebrium experienced a rapid remodeling of the heart, resulting in a statistically significant reduction of left ventricular mass, as well as a marked improvement in the initial phase of left ventricular diastolic filling. Additionally, in several pre-clinical studies, alagebrium has been shown to reduce the thickening of the left ventricle and induce a reverse remodeling of the heart.

Erectile Dysfunction

ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual intercourse. ED has been reported to affect as many as 20 to 30 million men in the United States and 152 million men worldwide, according to the National Institutes of Health. The risk for ED increases progressively with advancing age, with an estimated 54% of men ages 65 to 70 reporting some degree of impotence. It is believed that 85% to 90% of ED cases are related to a physical or medical condition, while 10% to 15% are due to psychological causes.

Many studies have identified ED as an early indicator of cardiovascular diseases, including hypertension, heart attack and stroke, and point to the underlying dysfunction of the arteries and vascular system as a principal

cause. ED is commonly associated with a number of other conditions frequently occurring in aging men, including enlarged prostate, hardening of the arteries, high cholesterol and diabetes.

An estimated 30% to 40% of diabetic and aged patients with ED do not receive benefit from currently available drugs, such as the PDE5 inhibitors, and patients with diabetes or severe vascular disease are among the most refractory to such treatments. This occurs, in part, because the corpus cavernosum, the structure in the penis that acts as an expandable reservoir for blood, is unable to properly dilate due to the accumulation and crosslinking of A.G.E.s. A.G.E.s have been demonstrated to impair erectile function in diabetes by affecting the functional capabilities of the corpus cavernosum and by interfering with the production of nitric oxide needed to maintain an erection. In October 2004, we announced the presentation of a pre-clinical study that demonstrated the ability of alagebrium to significantly improve erectile function, as well as decrease A.G.E. levels. In addition, alagebrium normalized other diabetes-induced pathologies associated with ED, an effect not seen with PDE5 inhibitors. According to the investigative team, these data are unlike results for currently marketed ED drugs in similar experiments.

Analysts estimate that the current ED market of around $1.8 billion a year could rise to total impotence drug sales of around $6 billion over the next eight years, split between currently-marketed ED drugs and other second-generation treatments.

Complications of Diabetes

A significant portion of diabetic individuals develops cardiovascular diseases and other complications due to the high levels of blood glucose and A.G.E.s within the body. According to the American Diabetes Association, heart disease is the leading cause of diabetes-related deaths. Heart disease death rates are two to four times higher in adults with diabetes than adults without diabetes. The risk of stroke is also two to four times higher in those with diabetes.

The Diabetes Control and Complications Trial, a multi-center clinical trial conducted by the National Institutes of Health, demonstrated that elevated blood glucose levels significantly increase the rate of progression of blood vessel, kidney, eye and nerve complications from diabetes. More than 50% of people with diabetes in the United States develop diabetic complications that range from mild to severe.

Kidney Disease

Kidney disease is a significant cause of morbidity and mortality in patients with Type 1 and Type 2 diabetes. It is a chronic and progressive disease that affects approximately one-third of patients with Type 1 diabetes. Approximately 10% to 15% of patients with Type 2 diabetes develop kidney disease. One of the early signs of kidney damage is microalbuminuria (characterized by leakage of small amounts of protein into the urine), which progresses to overt nephropathy (characterized by leakage of large amounts of protein into the urine) and ultimately to end-stage renal disease. Diabetes is the leading cause of kidney failure in the United States.

Other Markets of Opportunity

A.G.E.s have been shown to cause or contribute to many medical disorders. In addition to our ongoing clinical studies in systolic hypertension, heart failure and ED, we have early research studies focused on atherosclerosis; Alzheimer's disease; photoaging of the skin; eye diseases, including AMD and glaucoma; and diabetic complications, including renal diseases. We continue to evaluate potential indications for our compounds.

OUR TECHNOLOGY: THE A.G.E. PATHWAY IN AGING AND DIABETES

The harmful consequences of A.G.E. formation in man was proposed in the 1980's by our scientific founders as an outgrowth of a research effort focused on diabetes. The foundation for our technology is the experimental evidence that intervention along the A.G.E. pathway provides significant benefit in slowing or reversing the development of serious diseases in the diabetic and aging populations. We are the pioneers in A.G.E. technology, and we have built an extensive patent estate covering our discoveries and compounds.

A.G.E.s are permanent structures that form when simple sugars, such as glucose, bind to the surface of proteins. As the body ages, A.G.E. complexes form on proteins continuously and naturally, though slowly

throughout life, at a rate dependent upon glucose levels and on the body's natural ability to clear these pathological structures. A.G.E. complexes subsequently crosslink to other proteins. The A.G.E. crosslink has been found to be unique in biology and is prevalent in animal models of aging and diabetes. Scientific literature suggests that the formation and subsequent crosslinking of A.G.E.s is an inevitable part of the aging process and diabetes that leads to

the progressive loss of flexibility and function in various tissues, blood vessels and organs.

The formation and crosslinking of A.G.E.s is a well-known process in food chemistry called the Maillard Reaction. The browning and toughening of food during the cooking process occurs, in part, as a result of the formation of A.G.E. complexes between sugars and the amino acids of proteins.

The A.G.E. pathway may provide the scientific explanation for how and why many of the medical complications of the aging process occur with higher frequency and earlier in life in diabetic patients. Diabetic individuals form excessive amounts of A.G.E.s earlier in life than do non-diabetic individuals, due primarily to higher levels of blood sugar. For this reason, diabetes may be viewed as an accelerated form of aging.

A.G.E.s and A.G.E. crosslinks are considered to be likely causative factors in the development of many age-related and diabetic disorders. For example, proteins in the body, such as collagen and elastin, which play an important role in maintaining the elasticity of the cardiovascular system, are prime targets for A.G.E. crosslinking. This stiffening process can impair the normal function of contractile organs, such as blood vessels, which depend on flexibility for normal function. A loss of flexibility of the vasculature is associated with a number of cardiovascular disorders, including systolic hypertension, diastolic dysfunction, LVH and heart failure itself, as well as ED and other diabetic complications.

In addition to the fibrosis and stiffening of tissues and organs throughout the body, A.G.E.s have been shown to contribute to disease by adversely altering multiple inflammatory and metabolic pathways. A.G.E.s can lead to pathologic alterations commonly associated with diabetic nephropathy, retinopathy and alterations in molecules that accelerate atherosclerosis.

We incurred research and development expenditures of $10,147,000, $9,930,000 and $14,992,000 for the years ended December 31, 2004, 2003 and 2002, respectively.

A.G.E. Crosslink Breakers

A.G.E. Crosslink Breakers have the potential to treat a number of medical disorders where loss of flexibility or elasticity leads to a loss in function. Our lead clinical candidate, alagebrium, has demonstrated the ability to reverse tissue damage and restore function to the cardiovascular system in Phase 2 clinical studies in cardiovascular compliance, systolic hypertension and DHF. In a pre-clinical rat model of diabetes, alagebrium has demonstrated the ability to restore erectile function. Additionally, we are evaluating the development of several compounds in the breaker class for other indications where A.G.E. crosslinking leads to abnormal function.

We have identified 17 potential chemical classes of A.G.E. Crosslink Breakers, and have a library of more than 650 compounds.

Alagebrium

Alagebrium is a small, easily synthesized compound with a rapid mode of action. It is well absorbed from an oral tablet formulation. The compound is under Phase 2 clinical evaluation in systolic hypertension, heart failure and ED. It is being evaluated in various pre-clinical models to assess its safety and potential in a number of other disease states.

CURRENT CLINICAL STUDIES

As announced in February 2005, based on initial findings from a

pre-clinical toxicity study that provided direction for further analysis, we have voluntarily and temporarily suspended enrollment into each of the clinical studies described in this section, pending receipt of additional pre-clinical data. All trials are ongoing, and currently enrolled patients are permitted to continue treatment with alagebrium. Prior to resuming enrollment of any new patients into any of our clinical studies, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA. We cannot predict at this time when enrollment in our clinical studies will resume, if ever.

SPECTRA

In March 2004, we initiated SPECTRA, a double-blind, placebo-controlled Phase 2b clinical trial in patients with systolic hypertension. SPECTRA is designed to evaluate alagebrium's ability to lower systolic blood pressure in patients with a systolic blood pressure reading of greater or equal to 145 mm Hg, building upon positive data from previous Phase 2 trials. Alagebrium's activity in prior clinical trials demonstrated the drug's safety and ability to lower systolic blood pressure and pulse pressure in aging and diabetic patients, especially in the difficult-to-treat hypertensive patient population with blood pressure measured by ABPM monitoring.

In SPECTRA, approximately 400 patients are expected to be enrolled at over 70 clinical sites throughout the United States. The trial includes male and female patients who are at least 45 years of age. Recruited patients undergo a run-in phase during which they are stabilized on hydrochlorothiazide, a commonly-used diuretic. They then receive alagebrium tablets or placebo once a day for 12 weeks.

SPECTRA is designed to further extend the range of effective dosing defined in previous Phase 2 testing. The trial consists of four treatment arms, comprising three different dose levels of alagebrium (10, 50 or 150 mg) or placebo. Patients enrolled in the trial must have systolic blood pressure of greater than or equal to 145 mm Hg as measured by ABPM, as well as additional qualifications. Automated office blood pressures as well as ABPM pressures are taken at scheduled time points. The primary measure of efficacy will be the change from baseline in mean 24-hour systolic ABPM pressure after 12 weeks of dosing (as compared to placebo). Secondary endpoints will include changes in diastolic, pulse and arterial pressures.

While SPECTRA is ongoing, we have voluntarily and temporarily suspended the enrollment of new patients into the trial. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment of new patients into any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA.

PEDESTAL

In April 2004, we initiated PEDESTAL, a Phase 2a study being conducted at Baylor Heart Clinic in Houston. PEDESTAL is designed to continue evaluating the potential effects of alagebrium on diastolic dysfunction and left ventricular mass in patients with significant heart failure. In the previously completed Phase 2a DIAMOND study, treatment with alagebrium resulted in an unprecedented reduction in left ventricular mass within a 16-week treatment period, as well as a marked improvement in the initial phase of left ventricular diastolic filling and improvement in quality of life.

PEDESTAL is an open-label exploratory study to determine the effects of

alagebrium at two oral dosages (35 mg once a day or 210 mg twice daily) for 6, 12, 16 and 24 weeks on diastolic function and left ventricular mass in 20 patients diagnosed with systolic heart failure and diastolic dysfunction. Safety and quality of life are also being evaluated. The study includes men and women at least 30 years of age with or without diabetes, who are classified as having grade II to IV heart failure under the New York Heart Association guidelines. The primary endpoints, which include quantification of left ventricular mass and complete Doppler evaluation of changes in diastolic function, are again designed to look at the therapeutic remodeling capability of alagebrium. Secondary endpoints include a quality of life assessment as measured by the Minnesota Living With Heart Failure Questionnaire.

In December 2004, we announced that preliminary data from the initial 14 (of planned 20) patients indicate trends consistent with positive data from the DIAMOND study. While patients in PEDESTAL cannot be compared directly with those from DIAMOND (patients in PEDESTAL have impaired ejection fraction, larger hearts and are sicker overall), treatment with alagebrium appears to have important and consistent effects in both patient groups. While PEDESTAL is ongoing, we have voluntarily and temporarily suspended the enrollment of new patients into the study. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment of new patients into any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA.

JHU Study in Endothelial Dysfunction

In February 2004, we initiated a Phase 2a clinical study to evaluate the potential effects of alagebrium on endothelial dysfunction at JHU under grants from the National Heart, Lung and Blood Institute and the Society of Geriatric Cardiology. This academic study is an additional component to our ongoing Phase 2 studies in systolic hypertension and heart failure, and will help further elucidate alagebrium's mechanism of action in these indications.

The endothelium, a single-cell lining of the arteries that acts as an interface between the blood and arterial wall, is impaired in many cardiovascular conditions. Endothelial damage, and the resulting inability of smaller vessels to react to changes in blood pressure and flow, can be a predictor of present and future cardiovascular disease. Recent evidence suggests that when arteries become stiffer, endothelial function is worsened even when the endothelial cells themselves are normal. The loss of vascular tone due to the interaction between arterial stiffening and endothelial function may be important in explaining why stiff arteries are a major risk factor for cardiovascular disease.

The JHU endothelial study is designed to enroll approximately 25 patients, male or female who are 50 years of age or greater, with systolic hypertension (systolic blood pressure of greater than 140 mm Hg and a diastolic blood pressure of less than 95 mm Hg). Patients are receiving 210 mg of alagebrium twice daily for eight weeks, preceded by three weeks of twice daily placebo run-in dosing. The primary purpose of the study is to determine whether increasing arterial elasticity by breaking A.G.E. crosslinks improves endothelial function as assessed by evaluating vessel relaxation and biomarkers of endothelial function.

In December 2004, we announced positive findings from an interim analysis of this study. These data are showing strong trends in key measures relating to improvements in carotid and brachial artery stiffness based on a series of advanced non-invasive measurements. An initial group of patients has completed

the study, and data are expected to be presented in the first half of 2005. While the JHU study is ongoing, we have voluntarily and temporarily suspended the enrollment of new patients into the study. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment in any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA.

EMERALD

In January 2005, we initiated a Phase 2a study to evaluate the potential effects of alagebrium in ED. EMERALD will assess the ability of alagebrium to restore erectile function in diabetic patients with moderate to severe ED who achieve limited benefit from current treatment with PDE5 inhibitors, the first class of orally-active compounds approved for the treatment of ED. In a pre-clinical rat model of diabetes, alagebrium has demonstrated an ability to restore erectile function through what appears to be a unique mechanism of action and thus may offer significant potential as an adjunctive treatment for diabetic ED.

EMERALD is a randomized, double-blind, placebo-controlled Phase 2a pilot study being conducted under the direction of Wayne J.G. Hellstrom, M.D., Professor of Urology at Tulane University School of Medicine and an author of many of the seminal studies in ED. Approximately 40 male diabetic patients age 18 to 70 will be enrolled and randomized to receive oral doses of either alagebrium (200 mg once daily) or placebo tablets for a 16-week period in conjunction with their PDE5 inhibitor therapy. The primary endpoint of the study will be based on the International Index of Erectile Function questionnaire. Secondary endpoints of efficacy will be self-reported improvement in erections (according to a Global Assessment Question) and measurements of change from baseline in penile blood flow. While EMERALD is ongoing, we have voluntarily and temporarily suspended the enrollment of new patients into the study. We expect that decisions regarding resumption of enrollment will be made upon receipt of additional pre-clinical data. Prior to resuming enrollment of new patients into any of our clinical studies of alagebrium, we intend to review all relevant findings with appropriate oversight entities, including our DMC, IRBs and the FDA.

COMPLETED CLINICAL STUDIES

SAPPHIRE/SILVER

The Phase 2b SAPPHIRE/SILVER trial evaluated the effectiveness of alagebrium in approximately 770 patients having elevated systolic blood pressure with or without LVH. The trial was dose-ranging, double-blind, placebo-controlled and conducted at over 60 sites in the United States. In May 2004, the detailed findings from a

post hoc analysis of the SAPPHIRE/SILVER trial were presented at the American Society of Hypertension or ASH Nineteenth Annual Scientific Meeting. These data, which were subsequently published in a supplement to the December 15, 2004 issue of the American Journal of Hypertension, demonstrated that treatment with alagebrium, as recorded by ABPM, resulted in a significant reduction in systolic blood pressure in patients that are traditionally difficult to treat.

Highlights of the SAPPHIRE/SILVER data presented include:

- Alagebrium treatment resulted in highly significant reduction of systolic blood pressure in patients with a baseline 24-hour

ambulatory systolic blood pressure of 140 mm Hg or greater. These patients had uncontrolled blood pressure despite the continuation of their existing anti-hypertensive medications.

- In this patient population, significant efficacy at the best dose (35 mg once a day) was persistent and resulted in an average drop in systolic blood pressure of approximately 6 mm Hg vs. placebo (p