ALTEON INC /DE
Form 10-K
March 30, 2006

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, 2005, 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
Preferred Stock Purchase Rights	American Stock Exchange

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

NONE

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes [ ] No [X]

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes [ ] No [X]

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 a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one):
Large accelerated filer [ ] Accelerated filer [ ] Non-accelerated filer [X]

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes [ ] No [X]

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 ($0.22 per share), as of June 30, 2005, was $12,736,517.

At March 1, 2006, 57,996,711 shares of the Registrant's common stock, par value $.01 per share, were outstanding.

Documents Incorporated By Reference

None.

PART I

ITEM 1. BUSINESS.

OVERVIEW

We are a product-based biopharmaceutical company engaged in the development of small molecule drugs to treat and prevent cardiovascular disease and diabetes. We identified several promising product candidates that we believe represent novel approaches to some of the largest pharmaceutical markets. We have advanced one of these products into Phase 2 clinical trials.

Our lead drug candidate, alagebrium chloride or alagebrium (formerly ALT-711), is a product of our drug discovery and development program. Alagebrium has demonstrated potential efficacy in two clinical trials in heart failure, as well as in animal models of heart failure, nephropathy, hypertension and erectile dysfunction (ED). It has been tested in approximately 1,000 patients in a number of Phase 1 and Phase 2 clinical trials. Our goal is to develop alagebrium in diastolic heart failure (DHF). This disease represents a rapidly growing market of unmet need, particularly common among diabetic patients, and alagebrium has demonstrated relevant clinical activity in two Phase 2 clinical trials.

We are in the process of preparing to submit an investigational new drug application (IND) to the Division of Cardio-Renal Drug Products (the Cardio-Renal division) specifically for alagebrium in heart failure, in order to expand our clinical program in this therapeutic area. However, any continued development of alagebrium by us is contingent upon our entering into strategic collaboration agreements for this product candidate which, among other things,

would be required to include funding for product development.

In June 2005, our SPECTRA (Systolic Pressure Efficacy and Safety Trial of Alagebrium) Phase 2b trial in systolic hypertension was discontinued after an interim analysis found that the data did not indicate a treatment effect of alagebrium and we have ceased development of alagebrium for this indication.

Also, in June 2005, we announced that we had submitted preclinical toxicity data on alagebrium to two divisions of the United States Food and Drug Administration's, or FDA's, Center for Drug Evaluation and Research (CDER), specifically the Division of Cardio-Renal Drug Products and the Division of Reproductive and Urologic Drug Products (the Reproductive/Urologic division). The preclinical toxicity data were submitted in support of our view that liver alterations previously observed in rats, and reported in December 2004, were related to the male rat metabolism and not to genotoxic pathways. Subsequent preliminary data on liver alterations in rats had caused us to voluntarily suspend enrolling new patients into all of our alagebrium clinical trials in February 2005.

Following review of the rat liver data, the Cardio-Renal division allowed us to proceed with the development of alagebrium in cardiovascular indications. The Reproductive/Urologic division placed on clinical hold further enrollment in the EMERALD (Efficacy and Safety of AlagebriuM in ERectile Dysfunction in MALe Diabetics) study, our Phase 2a study of alagebrium in diabetic patients with erectile dysfunction, and requested further preclinical toxicity data, which we submitted in August 2005. After review of these data, the Reproductive/Urologic division decided to maintain the clinical hold pending further preclinical testing. In January 2006, we announced that we had withdrawn the IND for the EMERALD study. We decided instead to commit our resources to the development of alagebrium in cardiovascular diseases. There can be no assurance that we will ever pursue the development of alagebrium for the ED indication.

In November 2005, we announced that data presented at the American Heart Association (AHA), Scientific Sessions from the Phase 2a PEDESTAL (Patients with Impaired Ejection Fraction and Diastolic Dysfunction: Efficacy and Safety Trial of ALagebrium) study in diastolic dysfunction demonstrated the ability of alagebrium to improve measures of diastolic function, including a significant reduction in left ventricular mass.

Also in November 2005, in conjunction with a presentation at the AHA, we announced positive findings from a Phase 2a study to evaluate the potential effects of alagebrium on endothelial dysfunction. Initiated in February 2004, the study was conducted at Johns Hopkins University (JHU) School of Medicine under grants from the National Heart, Lung and Blood Institute and the Society of Geriatric Cardiology.

As a result of having withdrawn the IND for the EMERALD study, there is no clinical hold remaining on alagebrium from any division of the FDA. The FDA has never placed a clinical hold on our protocols in cardiovascular diseases, which are under the oversight of CDER's Division of Cardio-Renal Drug Products.

We are primarily focused on fundraising activities and exploring strategic relationships to support our development programs. During 2005, as part of these efforts, we engaged an investment banking firm to help us identify potential strategic options for the company. Those efforts are underway. At the present time, we have significantly curtailed all product development activities of alagebrium due to the absence of sufficient financial resources to continue its development.

We were incorporated in Delaware in October 1986. Our headquarters are located at 6 Campus Drive, Parsippany, New Jersey 07054. We maintain a web site at www.alteon.com and our telephone number is (201) 934-5000. 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, are available to you free of charge through the "Investor Relations" section of our website as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the Securities and Exchange Commission.

PATHWAYS

The A.G.E. Pathway

Advanced Glycation End-Products (A.G.E.) are glucose/protein complexes and are formed by a reaction between circulating blood glucose molecules and proteins. They appear to induce protein crosslinking. These pathological complexes affect the structural chemistry of tissues and organs, resulting in increased stiffness and fibrosis, as well as impaired flexibility and compromised function. 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 diastolic dysfunction, left ventricular hypertrophy (LVH) and heart failure itself, as well as other diabetic complications.

In addition to their role in promoting 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 processes that accelerate atherosclerosis.

In recent years, our research and drug development activities targeting the A.G.E. pathway have focused on the development of A.G.E. Crosslink Breakers and A.G.E. Formation Inhibitors. 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 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 to have entered 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 tissues and organs, thereby potentially reversing the damage caused by aging and diabetes.

OUR BUSINESS STRATEGY

Our strategy has been to develop drug candidates from our proprietary portfolio of new chemical entities with a goal to develop compounds to address

large medical needs that are unmet by existing therapies. We may seek, as appropriate, to selectively in-license clinical stage compounds and as appropriate to out-license or co-develop some drug candidates with corporate partners. Assuming we continue the clinical development of alagebrium, we may elect to retain development and marketing rights for one or several indications, while at the same time continuing to evaluate potential corporate partnerships for the further development and ultimate marketing of the compound. In addition to these pipeline products, 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.

In August 2005, in order to enable us to move forward with the continued development of alagebrium, we announced that we had engaged the services of Burrill & Company (Burrill) to assist in developing and identifying options designed to diversify our portfolio of product candidates and to enhance the ability to raise financing in the future. Such potential transactions include the acquisition of technologies and product programs, licensing opportunities, the sale to or merger into another company, and debt and equity financing. Burrill has identified a number of potential transactions and we are currently in discussions with one company regarding the acquisition of a cardiovascular therapeutic technology. We are also in discussions with Genentech regarding the restructuring of their preferred stock position in the Company. There can be no assurances that we will be able to consummate a transaction. However, as a result of our current financial situation, any continued development of alagebrium by us is contingent upon our entering into one or more strategic collaboration agreements for this product candidate which, among other things, would be required to include funding for product development.

MARKETS OF OPPORTUNITY

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

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 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. Data

presented from the Phase 2a PEDESTAL study in diastolic dysfunction demonstrated the ability of alagebrium to improve measures of diastolic function.

Left ventricular hypertrophy, refers to the thickening of the left ventricle that can occur progressively with hypertension and DHF. 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 and DHF. Patients who were treated with alagebrium have 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 preclinical studies, alagebrium has been shown to reduce the thickening of the left ventricle and induce a reverse remodeling of the heart.

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 increasingly stiff, 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. Alagebrium has been shown to significantly improve endothelial function.

Complications of Diabetes

A significant portion of diabetic individuals develop 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 and approximately 10-15% of patients with Type 2 diabetes. 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.

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

The harmful consequences of A.G.E. formation in man were 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 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 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 diastolic dysfunction, LVH and heart failure itself, as well as ED and other diabetic complications.

In addition to their role in promoting 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 $9,074,000, $10,147,000 and $9,930,000 for the years ended December 31, 2005, 2004 and 2003, 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 distensibility and DHF. 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 several potential chemical classes of A.G.E. Crosslink Breakers, and have an extensive library of 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 has completed several Phase 2 studies and is being evaluated in various preclinical models to assess its safety and potential in a number of other disease states.

CURRENT CLINICAL STUDIES

CLINICAL AND PRECLINICAL DEVELOPMENT OF LEAD COMPOUND ALAGEBRIUM

Our current priorities are to continue the Phase 2 clinical development of alagebrium in heart failure. If we are able to obtain sufficient funding to do so, through a collaboration or otherwise, we hope to restart our clinical studies of alagebrium in heart failure in late 2006 or early 2007.

ALAGEBRIUM: AN A.G.E. CROSSLINK BREAKER

We plan to pursue development of alagebrium in high potential cardiovascular indications such as heart failure, after recent data presented at the American Heart Association (AHA) Scientific Sessions in November 2005 demonstrated continued positive results of alagebrium in patients with cardiovascular disease. The AHA presentations included data from the Phase 2a PEDESTAL study in diastolic dysfunction in heart failure with impaired ejection fraction, as well as positive results from a Phase 2a study in endothelial function.

In addition to these and other Phase 2 clinical studies, we have also conducted a series of Phase 1 safety and dose escalation studies of alagebrium. These studies have thus far shown alagebrium to be safe and well tolerated in humans.

We are in the process of preparing an IND specifically in heart failure in order to expand alagebrium's clinical program in this therapeutic area. Based on the previous positive data in heart failure and endothelial dysfunction [see the discussions of the PEDESTAL, Johns Hopkins and DIAMOND (Distensibility Improvement And ReMOdeliNg in Diastolic Heart Failure) studies set forth below}, we are proposing an advanced multi-institutional Phase 2 study involving 200 patients with diastolic heart failure and diabetes, and hope to initiate this trial in late 2006 or early 2007. However, any continued development of alagebrium by us is contingent upon our entering into strategic collaboration agreements for this product candidate which, among other things, would be required to include funding for product development.

As a result of having withdrawn the IND for our EMERALD study, discontinued the SPECTRA trial and completed the PEDESTAL and Johns Hopkins endothelial dysfunction studies, all of which are described below, we have no subjects currently under protocol in any clinical study of alagebrium.

We continue to evaluate potential preclinical and clinical studies in other therapeutic indications in which alagebrium may address significant unmet needs. In addition to our anticipated clinical studies in heart failure, we have conducted early research studies focusing on atherosclerosis; Alzheimer's disease; photoaging of the skin; eye diseases, including age-related macular degeneration (AMD), and glaucoma; and other diabetic complications, including

renal diseases.

CLINICAL STUDIES

PEDESTAL

In November 2005, we announced that data presented at the American Heart Association Scientific Sessions from the Phase 2a PEDESTAL (Patients with Impaired Ejection Fraction and Diastolic Dysfunction: Efficacy and Safety Trial of ALagebrium) study in diastolic dysfunction demonstrated the ability of alagebrium to improve measures of diastolic function, including a significant reduction in left ventricular mass.

PEDESTAL was 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 were also evaluated. The study included men and women at least 30 years of age with or without diabetes, who were 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, were 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.

The PEDESTAL data indicated trends consistent with positive data from our previous heart failure study, DIAMOND. While subjects in PEDESTAL could not be compared directly with those from DIAMOND, because those in PEDESTAL had impaired ejection fraction, larger hearts and were sicker overall, treatment with alagebrium appeared to have important and consistent effects in both patient groups.

The AHA poster presentation, entitled "Improvements in Diastolic Function Among Patients with Advanced Systolic Heart Failure Utilizing Alagebrium, an Oral Advanced Glycation End-product Crosslink Breaker," describes the key findings from PEDESTAL. Twenty-two subjects were treated at the Baylor College of Medicine in an open-label, two-dose (35 mg and 210 mg bid) regimen and followed by echocardiography. The data revealed significant improvements from a combined analysis of both dose groups in Doppler measures of diastolic function, including the early/late atrial filling phase ratio, deceleration time, isovolumetric relaxation time and resulting reduction of left atrial pressure. In addition, some patients achieved regression of left ventricular mass and left ventricular end-diastolic volume.

Johns Hopkins University Study in Endothelial Dysfunction

Also in November 2005, in conjunction with a presentation at the AHA, we announced positive findings from a Phase 2a study to evaluate the potential effects of alagebrium on endothelial dysfunction. Initiated in February 2004, the study was conducted at Johns Hopkins University (JHU) School of Medicine under grants from the National Heart, Lung and Blood Institute and the Society of Geriatric Cardiology.

The JHU endothelial study was designed to enroll male or female subjects 50 years of age or more, with systolic hypertension (defined as having systolic blood pressure of greater than 140 mm Hg and a diastolic blood pressure of less

than 95 mm Hg). Subjects received 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 was 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 the study, "Improved Flow-Mediated Arterial Vasodilation by Advanced Glycation Crosslink Breaker, Alagebrium Chloride (ALT-711), in Older Adults with Isolated Systolic Hypertension," 13 adults with isolated systolic hypertension on stable antihypertensive therapy received a 2-week placebo run-in followed by 8 weeks of oral alagebrium. Data measurements were taken after placebo run-in and after 8 weeks of therapy. Treatment with alagebrium reduced carotid augmentation index (AI), a measure of arterial stiffness, by 37% and carotid augmented pressure, whereas pulse wave velocity (PWV) was unaltered. Thus, overall arterial stiffening, as reflected by AI, was markedly reduced by alagebrium therapy. Heart rate, brachial arterial pressures and brachial artery distensibility measures were unaltered by alagebrium therapy. However, alagebrium significantly improved flow-mediated dilation, a measure of endothelial function, by 102%. Alagebrium therapy improved peripheral artery endothelial function, independent of changing local arterial distensibility, suggesting a new mechanism through which alagebrium may act on A.G.E.s which directly impair dynamic vascular function in addition to its apparent effect on A.G.E.s impacting the structural aspects of arteries.

SPECTRA

In June 2005, SPECTRA, a Phase 2b trial in systolic hypertension, was discontinued after an interim analysis of data from the first 190 out of an anticipated 400 patients in the trial did not indicate a treatment effect of alagebrium. Accordingly, we have ceased development of alagebrium for this indication.

SAPPHIRE/SILVER

The Phase 2b SAPPHIRE/SILVER (Systolic And Pulse Pressure Hemodynamic Improvement by Restoring Elasticity/Systolic Hypertension Interaction with Left VEntricular Remodeling) 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 an analysis of the SAPPHIRE/SILVER trial were presented at the American Society of Hypertension (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 automatic blood pressure measurement (ABPM), resulted in a significant reduction in systolic blood pressure in patients that are traditionally difficult to treat.

The findings supported the hypothesis that alagebrium works best in patients with more serious baseline hypertension via a mechanism of action unlike any currently marketed high blood pressure drug.

We announced the initial results of the SAPPHIRE/SILVER trial in July 2003. The pre-specified primary endpoint of this trial, reduction of systolic blood pressure by office cuff pressure measurement at the highest of the four active dose levels, 210 mg per day, did not demonstrate statistical significance as compared to placebo. The data analysis was confounded by a 6 to 10 mm Hg drop in

systolic blood pressures in all arms of the SAPPHIRE/SILVER trial, including placebo, during the first two weeks after patient randomization. However, subjects in the SAPPHIRE "intent-to-treat" population demonstrated efficacy net of placebo, in the 2 to 3 mm Hg range by cuff pressure, at the lower end of the alagebrium dosing range. As reported at that time, a pre-specified secondary analysis of ABPM measurements in subjects who completed the study demonstrated a blood pressure lowering effect at lower doses of about 4 mm Hg net of placebo. Importantly, there was no significant placebo effect noted in the ABPM measurements, and that data were presented at the ASH meeting in May 2004, as noted above.

DIAMOND

In January 2003, we announced positive results from an analysis of the first 17 subjects in the Phase 2a DIAMOND clinical study, evaluating the potential effects of alagebrium in patients with diastolic dysfunction in diastolic heart failure. The study was conducted at Wake Forest University Baptist Medical Center and the Medical University of South Carolina in subjects at least 60 years of age with isolated DHF.

In the DIAMOND study, 23 subjects received 210 mg of alagebrium twice daily on an open-label outpatient basis for 16 weeks in addition to their current medications. Primary endpoints included changes in exercise tolerance and aortic stiffness. Effects on left ventricular hypertrophy, diastolic filling and quality of life were also assessed. Those who received alagebrium for 16 weeks experienced a rapid remodeling of the heart, resulting in a statistically significant reduction in left ventricular mass as well as a marked improvement in the initial phase of left ventricular diastolic filling. Additionally, the drug was well tolerated and had a positive effect on quality of life. Measurements of exercise tolerance and aortic distensibility proved to be more variable than anticipated for a study of this size and were not reportable.

EMERALD

In January 2005, we initiated a Phase 2a study to evaluate the potential effects of alagebrium in ED. EMERALD was designed to assess the ability of alagebrium to restore erectile function in approximately 40 male diabetic subjects 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 preclinical rat model of diabetes, alagebrium had demonstrated an ability to restore erectile function through what appeared to be a unique mechanism of action that might offer significant potential as an adjunctive treatment for diabetic ED.

In January 2006, we announced that we had withdrawn the IND for the EMERALD study because the Reproductive/Urologic Division had required additional preclinical testing of the drug before allowing Phase 2a

testing to proceed, and we decided instead to commit resources to the development of alagebrium in cardiovascular diseases. There can be no assurance that we will ever pursue the development of alagebrium for the ED indication.

In June 2005, we announced that we had submitted pre-clinical toxicity data on alagebrium to two divisions of the FDA's Center for Drug Evaluation and Research, specifically the Division of Cardio-Renal Drug Products and the Division of Reproductive and Urologic Drug Products. The pre-clinical toxicity data were submitted in support of our view that liver alterations previously

observed in rats, and reported in December 2004, were related to the male rat metabolism and not to genotoxic pathways. Preliminary data on liver alterations in rats had caused us to voluntarily suspend enrolling new patients into all of our alagebrium clinical trials, including EMERALD, in February 2005.

Following review of the rat liver data, CDER's Division of Reproductive and Urologic Drug Products placed on clinical hold further enrollment in the EMERALD study, our Phase 2a study of alagebrium in diabetic patients with erectile dysfunction, and requested further pre-clinical toxicity data, which we submitted in August 2005. After review of these data, the Reproductive/Urologic division decided to maintain the clinical hold pending further pre-clinical data.

Phase 2a Cardiovascular Compliance Study

In January 2001, we announced successful results from a Phase 2a clinical study of alagebrium evaluating the effects of the compound on cardiovascular elasticity and function. This study, conducted at nine United States clinical sites, was a double-blind, placebo-controlled study evaluating the safety, efficacy and pharmacology of alagebrium.

Study results showed that subjects who received alagebrium had a statistically significant (p