

CorCap[®] Cardiac Support Device (CSD) (P040049)
Acorn Cardiovascular, Inc.

CLINICAL STUDY SUMMARY

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ATTACHMENT LETTER FROM DR. PATRICK MCCARTHY

1.0 INTRODUCTION

1.1 Public Health Need

Heart failure is a complex clinical syndrome due to number of conditions such as coronary artery disease, valvular heart diseases, hypertensive heart disease or idiopathic cardiomyopathy. All conditions of heart failure include shortness of breath, fatigue and fluid retention. Because of the fluid retention, systolic heart failure is often called congestive heart failure (CHF). CHF has prominent effects on quality of life and greatly increases the risk of death.

Heart failure due to systolic dysfunction is a major worldwide threat to public health. Half a million people are diagnosed with CHF yearly and the annual rate of hospitalizations has nearly doubled in the last 10 years. CHF is responsible for 300,000 deaths annually in the US. The prognosis following a diagnosis is poor, with nearly 50% mortality by 5 years after diagnosis. The estimated direct and indirect cost of heart failure in the US for 2006 is \$29.6 billion.¹

1.2 Causes and Treatment of Heart Failure

Systolic heart failure has a number of causes, of which cardiac ischemia is the most common. Other common causes include cardiomyopathies, chronic hypertension, alcoholism, and myocarditis. Impaired systolic dysfunction has a number of physiologic consequences. In order to support the body's needs for cardiac output, the heart dilates. Although dilation will help to increase cardiac output, a number of other processes occur that result in abnormal cardiac muscle remodeling. Such processes include changes in adrenergic responses, myocyte hypertrophy, alterations in the extracellular matrix, apoptosis and abnormal expression of stretch response proteins. Cardiac muscle hypertrophy, one of the consequences of cardiac remodeling, can further impair systolic function. The combination of dilation and hypertrophy can lead to a more spherical left ventricular shape. As a result of dilation and hypertrophy, the heart experiences increased cardiac muscle wall stress and increases in left ventricular end-diastolic pressures (LVEDP). The increase in LVEDP causes increased capillary pressure in the lungs, resulting in shortness of breath and fluid retention.

Pharmacotherapy for systolic heart failure aims to reduce impedance and block neurohormonal vasoconstrictor systems (ACE inhibitors and beta blockers), improving systolic function (digoxin and other inotropic agents), and reduce fluid retention (diuretics). Despite optimal pharmacotherapy, however, systolic dysfunction commonly progresses, resulting in worsening symptoms. Patients who initially experienced shortness of breath and fatigue during moderate exercise (New York Heart Association Class II) progress to experience the same symptoms during mild exercise (Class III) or at rest (Class IV).

Treatment options beyond standard pharmacotherapy for patients with advanced heart failure are limited. Some patients with valvular abnormalities may benefit from valve

replacement surgery. Patients with ischemic cardiomyopathies may benefit from stenting or coronary artery bypass grafting (CABG). Patients with prolonged QRS duration may benefit from cardiac resynchronization therapy (CRT). When severe, mechanical assist devices, continuous IV inotrope infusion, and heart transplant are treatment options. However, none of these treatments address cardiac remodeling, one of the fundamental causes of progressive worsening of cardiac function. Indeed, left ventricular remodeling may be the disease process itself.² Thus therapy specifically targeting remodeling is an important unmet need in heart failure treatment.

1.3 Early Studies

1.3.1 Animal Studies

Proof of concept studies were performed in 3 different animal models of heart failure. In the first model, heart failure was produced in the dog by injection of microspheres into the coronary arteries until ejection fraction was reduced to approximately 35%.³ The control animals demonstrated progressive increases in LV end diastolic volume, whereas the CorCap CSD group showed an actual reversal since there were significant decreases in LVEDV. Furthermore, LV ejection fraction (LVEF) decreased in the control group, whereas this pattern was reversed in the CSD treatment group.

A second model of heart failure utilizing high-rate pacing in sheep was used to confirm these positive findings. Power and colleagues reported that the CorCap CSD implant maintained or reduced heart size and increased LVEF, fractional shortening and peak positive dP/dt.⁴ These improvements were noted when the CorCap CSD was implanted either in moderate or more advanced heart failure.

Finally, consistent findings of reduced ventricular size and improved ventricular function were also reported in a sheep model of heart failure produced by ligation of coronary arteries.⁵ This model is different from the first two because LV dilation is very mild.

1.3.2 Clinical Studies

Safety studies of the CorCap CSD provided initial evidence of safety and effectiveness, and supported progression to the pivotal trial stage. As part of safety studies conducted in Germany and Australia, 34 patients received the implant⁶ and were followed for up to 4 years.

During the course of the safety study, forty seven serious adverse events in twenty five patients and fifteen deaths were reported over 4 years of follow-up. None of the deaths were attributed to the CorCap CSD. In combination with safety data from Pilot and Run-in studies, these results led to two changes: Acorn's Safety Review Committee recommended a more conservative patient population and stricter device fitting instructions. Based on these recommendations, Acorn revised the inclusion and exclusion criteria, the Instructions for Use, and physician protocol training for future trials, including the pivotal trial.

Effectiveness data from these studies showed a positive clinical outcome in patients treated with the device. LVEDD decreased to a nadir at 6 months and was sustained at each follow-up time point. LVEF was significantly increased by 3 months and was maintained during long term follow-up. The improvement in cardiac structure and function was associated with a significant improvement in NYHA functional class and quality of life measures.

Furthermore, in a subgroup of 7 patients from this study who had a CorCap CSD implant concomitant with mitral valve repair, there was a significant reduction in LV mass ($p < 0.05$). A similar pattern was observed in the 7 patients with CorCap CSD-only implants ($p < 0.05$). Mass and volume were measured using contrast enhanced electron beam computerized tomography (EBT).⁷

These results were supported by data from an additional 85 patients who received the CorCap CSD in non-blinded pilot, run-in and surveillance studies conducted in Europe. No additional risks were identified from these studies, and adverse events were consistently reported as not device-related. Efficacy signals were consistent with the results seen in the safety studies.

1.4 Device Design

The CorCap CSD is designed to reduce cardiac wall stress (and thereby favorably impact cardiac remodeling in heart failure) by applying a gentle counterpressure of approximately 5 mm Hg to the left ventricle at the end of heart filling (diastole). Such a reduction of LVEDP may be beneficial in terms of reducing symptoms of heart failure and reducing the impact of increased LVEDP on the cardiac remodeling process. During heart emptying (systole), the device is designed to neither restrict cardiac motion nor exert pressure on the heart. The CorCap CSD is in part based on the finding that patients who underwent dynamic cardiomyoplasty, in which the latissimus dorsi muscle was wrapped around the heart and electrically stimulated, had an improvement in symptoms when the wrap was not stimulated. This observation led to the hypothesis that diastolic support, and not augmented systolic contraction, was responsible for the benefit.⁸ If true, there were many simpler methods of developing a synthetic “wrap” that did not require the complex surgery of the latissimus dorsi operation.⁵

1.5 Device Description

The CorCap CSD is a polyester mesh wrap that is placed around the heart and provides support to the heart’s structure and function. The wrap is designed to halt or reverse the progression of CHF.

The CorCap CSD is constructed from flat knit 100% polyester fabric and USP grade class I PTFE-coated polyester non-absorbable suture material. A pattern template is used to cut each CorCap CSD from a single piece of fabric. Seams and hems that result on a finished device are located on the outside of the device to create a smoother transition between the

CorCap CSD and the cardiac tissue. Bench testing of the device has demonstrated that it can constrain an end-diastolic design pressure of 50 mm Hg for in-excess of twenty-five years. The fabric supports tensile strength greater than 2.5 lbs/inch.

The CorCap CSD is offered in 6 sizes to accommodate various sized hearts. The implanting surgeon selects the device size based on preoperative estimates and intraoperative confirmation of patient heart size. Device size is chosen based on two parameters: length of the AV groove to the apex of the heart and the maximum circumference of the ventricular portion of the heart (surface).

1.6 Proposed Indications for Use

The safety and effectiveness of the CorCap CSD has been demonstrated in Acorn's original, 300 patient clinical study. However, the PMA as amended proposes a revised indication for use, based on the improved risk/benefit profile observed in a Focused Cohort from the full cohort.

The proposed intended use and indications for use for the CorCap CSD are:

The CorCap CSD is designed to provide ventricular support and reduce ventricular wall stress in patients with dilated cardiomyopathy and symptomatic heart failure. The CorCap CSD provides beneficial changes in cardiac structure as evidenced by a statistically significant reduction in left ventricular (LV) size and a significant change to a more elliptical shape. The CorCap CSD also provides a significant decrease in the need for additional major cardiac procedures associated with the progression of heart failure and a significant improvement in quality-of-life as measured by both the Minnesota Living with Heart Failure and the SF-36 questionnaires.

The CorCap CSD is indicated for use in adult patients who have been diagnosed with dilated cardiomyopathy and are symptomatic despite treatment with optimal heart failure medical management. Patients appropriate for this procedure have a dilated heart (indexed left ventricular end-diastolic dimension (LVEDDi) ≥ 30 and ≤ 40 mm/m²), and a LVEF $\leq 35\%$ (or LVEF $\leq 45\%$ if mitral valve repair or replacement is planned).

1.7 History of Clinical Study

The *Clinical Evaluation of the Acorn Cardiac Support Device Therapy in Subjects with Dilated Cardiomyopathy – A Randomized Trial in the United States and Canada* was initiated under an approved Investigational Device Exemption (IDE) (G990267) in June 2000, after a year of planning and collaborative discussion with the Food and Drug Administration (FDA's) Division of Cardiovascular Devices (DCD). Both Acorn and DCD recognized the challenge of designing a large-scale study for a heart failure device. As such, Acorn committed to working with DCD to refine the study design throughout the

course of the study. The result was an innovative study design using a composite endpoint to measure safety and effectiveness in a rigorous and clinically meaningful manner.

On February 16, 2001, Acorn met with DCD to present data from early studies performed in Europe, Australia and the United States and to present planned changes to the investigational protocol. Several months of follow-up discussion produced a revised study protocol, submitted to DCD as a supplement to the IDE. The revised design included modifications to inclusion/exclusion criteria and patient testing, and added a core lab (vs. site assessed) New York Heart Association (NYHA) baseline assessment of functional class using the Goldman survey.

On June 8, 2001, Acorn received non-conditional approval to expand the trial to the pivotal phase with 170 subjects at 20 sites using the revised study protocol. However, within this approval, DCD made several suggestions regarding the study design which were intended help demonstrate safety and effectiveness in a future PMA application (i.e., clinically meaningful). These suggestions included an alternate primary endpoint, increased sample size and increased follow-up. As a result, Acorn and DCD entered into several months of negotiation and discussion regarding how to implement these suggestions. It is important to note that negotiations about the study protocol were focused on the relative hierarchy of the data being collected, and not on the appropriate data to collect. It was therefore prudent for Acorn to continue data collection and study enrollment during these negotiations.

In October 2001, Acorn and DCD agreed to discontinue use of the Goldman NYHA analysis from the protocol, as the preliminary results produced by these surveys consistently misclassified patients with clear diagnostic evidence of advanced heart failure as NYHA Class I.

In November 2001, a conference call was held between Acorn and DCD in which a pivotal study design and sample size were agreed upon. At the conclusion of the call, the Director of DCD summarized the changes to the study design: to extend study follow-up from six months to one year, to expand the trial size to 180 subjects at 25 sites, to shift structural endpoints (left ventricular end diastole and systole diameter) from primary to secondary, and to adopt a composite primary endpoint. The resulting innovative study design used a composite ordinal endpoint based on death, major cardiac procedures indicative of progressive heart failure, and blinded assessment of change in NYHA classification to assess safety and effectiveness (since Goldman analysis would no longer be used, Acorn would develop an alternative blinded NYHA assessment method). Many primary endpoint alternatives were discussed, but, ultimately, DCD and Acorn agreed on this composite endpoint, which had been previously advocated for heart failure trials by Dr. Milton Packer.⁹

Acorn submitted the final supplement incorporating the agreed upon revisions on January 21, 2002, including a revised protocol which introduced a new methodology for conducting the core lab NYHA assessment. On February, 21, 2002, Acorn received a

conditional approval letter which cited 14 deficiencies, many of which were inconsistent with prior negotiations with DCD. In the letter, DCD raised for the first time the issues of whether to pool feasibility data with pivotal phase data and of how to address missing baseline NYHA assessment data for subjects enrolled prior to the pivotal phase. Most significantly, DCD changed its position on the sample size agreed upon in November 2001 and asked Acorn to increase the study size to 380 subjects.

On May 20, 2002, Acorn submitted an IDE supplement in response to the February 21, 2002 conditional approval letter. In the supplement, Acorn acquiesced to the DCD request for a larger sample size, and increased the study size to 300 subjects despite the lack of sound statistical basis for this sample size. On June 19, 2002, Acorn received a non-conditional approval letter for this supplement. By the time this study protocol was approved by the Institutional Review Board at each participating site, a total of 174 subjects had been enrolled who did not have a blinded core lab NYHA classification at baseline.

In June 2003, study enrollment was completed and Acorn began preparing a modular Pre-Market Approval (PMA) application. Acorn requested and received FDA approval for a Continued Access Program to allow patients to receive the CorCap CSD during the PMA review period. Continued Access is granted when there is a public health need for the device, or preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.¹⁰

On March 16, 2004, Acorn met with DCD to discuss Acorn's lingering concerns over how to account for patients with missing core lab NYHA classification at baseline. Acorn, still blinded to aggregate data at this time, proposed using site-assessed NYHA classification in the composite primary endpoint. DCD stated that they understood the issues but would not allow any change to the primary endpoint at that time. Acorn proceeded with submitting an IDE supplement on April 16, 2004 that updated the data analysis plan with minor changes but made no change to the analysis of the primary endpoint.

On May 19, 2004, DCD granted conditional approval to the April 16 IDE supplement, citing eight deficiencies. The most significant deficiency concerned the missing core lab NYHA classification data at baseline. FDA rejected as "not acceptable" a comparison of site NYHA assessment at baseline to core lab NYHA assessment at final follow-up (the approved analysis plan at that time), or a comparison of site NYHA assessment at both baseline and final follow up. Instead, FDA recommended that Acorn impute the missing core lab data based on other baseline characteristics, and provided model requirements. Thus, DCD reversed its position at the March 16 meeting and requested a change in the analysis of the primary endpoint. On May 28, 2004, Acorn submitted an IDE Supplement which addressed the eight deficiencies in FDA's May 19, 2004 letter (including a question for FDA regarding imputation precedents). FDA approved this supplement on July 1, 2004 and stated that Acorn should use "as many methods as you believe appropriate" to analyze the NYHA component of the primary endpoint, but did not provide the requested information regarding imputation. Accordingly, on August 6, 2004, Acorn provided a

formal IDE Supplement which stated Acorn's intent to follow FDA's recommendation in the May 19, 2004 letter and impute the missing blinded NYHA baseline data for 174 patients.

The clinical module of the PMA (P040049) was submitted on December 20, 2004 and the PMA was accepted for filing by DCD on January 13, 2005. The submission was granted expedited review status based on the determination that the CorCap CSD has the potential to provide treatment of a life-threatening or irreversibly debilitating condition.

On April 29, 2005, a Major Deficiency letter was issued by DCD. In response, amendments to the PMA were filed on May 3, May 17, May 19, and June 6, 2005.

On June 22, 2005, the Circulatory System Devices Advisory Panel convened and recommended against approval of the PMA with a vote of 9 to 4. The Advisory Panel members voting against approval provided the following reasons for their votes: lack of clinical outcome data; the number of patients with missing data (incomplete ascertainment); and safety concerns regarding potential long-term complications from placement of the device. It should be noted that the Advisory Panel statistician stated that she was unable to provide meaningful expert comment to her colleagues on the imputation method used by Acorn because she had not received sufficient information about the imputation methodology in advance of the meeting.

The Office of Device Evaluation (ODE) issued a not-approvable letter for the CorCap CSD PMA on August 12, 2005. The not-approvable letter identified three safety concerns and three effectiveness concerns.

FDA's three safety concerns were:

1. Risk of peri-operative death
2. Safety of re-operation after CorCap CSD implantation due to adhesions
3. Risk of long-term pericardial constriction

FDA's three effectiveness concerns were:

1. Missing data for the primary endpoint
2. The lack of statistical significance in any secondary endpoints
3. The absence of a specific patient population in which the device appears effective

FDA offered three options for amending the PMA to produce an approvable application. The options identified by ODE for additional data and information needed for an approvable application were to:

- A. Perform a post hoc analysis of the pivotal trial data set to exclude high risk patients, and thereby identify a patient population in which the benefits of the device more substantially outweigh the risks;
- B. Submit additional clinical experience from outside the US and re-analyze the current data set with outside of the United States (OUS) data to identify a patient population in which the device is reasonably safe and effective; or
- C. Identify a predicted patient population that will experience a greater risk-benefit ratio and “conduct an additional prospective study in this specific population, using historical controls from the existing data, to obtain a data set that demonstrates reasonable safety and effectiveness.”

Acorn accordingly prepared and submitted new data and information in a Major Amendment on October 25, 2005 (Amendment 5). This submission provided the additional data and information requested by ODE in Option (A) and provided a response to each of the six deficiencies cited by FDA in the not-approvable letter of August 2005, as well as addressed the concerns raised by the Circulatory System Devices Advisory Panel. In addition, Acorn proposed a postmarket study to address the safety concerns regarding potential long-term implications of placement of the device raised by the Advisory Panel.

On February 2, 2006, FDA issued a not-approvable letter for the amended PMA. Note that this letter did not provide the reasons for disapproval, as required by the regulations (21 CFR 814.45(b)). Although FDA had previously provided this approach as an option to Acorn to render the PMA approvable in the August 12, 2005 not-approvable letter, FDA now stated that the post hoc Focused Cohort analysis submitted by the Applicant was useful as a “promising hypothesis” in identifying a patient population in which “the device may be safe and effective” but that FDA required a “prospective study that clinically validates the risk-benefit profile” of the device in this patient population in order to render the PMA approvable.

Acorn disagrees that a second prospective, premarket study is necessary, given that the pivotal trial met its effectiveness and safety endpoints, and that concerns raised by FDA and the Advisory Panel have been adequately addressed by amendments to the PMA. Acorn submitted a request for the remaining scientific issues in dispute to be referred to the Medical Devices Dispute Resolution Panel, which was granted by FDA on June 7, 2006.

2.0 CLINICAL STUDY DESIGN

2.1 Summary

This study was a prospective, randomized controlled clinical trial of the Acorn CorCap Cardiac Support Device for the treatment of heart failure with systolic dysfunction with or without mitral valve disease. Subjects with heart failure with or without concomitant mitral valve disease requiring mitral valve repair or replacement (MVR) were randomly assigned to treatment with CorCap plus optimal medical therapy vs. medical therapy alone. Treatment subjects requiring MVR underwent MVR prior to placement of the CorCap device. Control subjects requiring MVR but assigned to medical therapy underwent only MVR. Subjects were followed for a minimum of one year after institution of assigned treatment. The full study protocol (Revision 8) is included in Appendix B of the Sponsor Panel Pack.

2.2 Objectives

The objectives of this study were to evaluate the safety and effectiveness of the CorCap device in patients with heart failure due to systolic dysfunction. The primary objective was to demonstrate functional status improvement at a minimum of 12 months after CorCap placement. One secondary objective was to evaluate the safety of CorCap placement in terms of survival and occurrence rate of adverse events compared to the control group. The other secondary objective was to demonstrate improvement in cardiac function and structure as measured by echocardiography and exercise testing.

2.3 Patient Population

The target population for CorCap placement is clinically stable patients with heart failure due to systolic dysfunction. Specific inclusion and exclusion criteria are described below. Note that whether potential study subjects met inclusion/exclusion criteria was verified by Acorn personnel prior to randomization.

2.3.1 Inclusion Criteria

To be included in the study, subjects had to meet all criteria listed in **Table 1**.

Table 1
CorCap Study Inclusion Criteria

1. Age 18-80 years
2. History of heart failure with dilated cardiomyopathy
3. On stable, optimal medical therapy for heart failure, including
 - Angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers
 - Diuretics / PRN
 - Beta blocker (unless intolerant) for ≥ 3 months*
 - No change in cardiac medications for > 1 month, except for diuretic adjustments**
4. All pre-enrollment testing within 1 month except where noted
5. Left ventricular end diastolic dimension (LVEDD) ≥ 60 mm or LVEDD index ≥ 30 mm/m²
6. Mitral regurgitation (MR) $< 2+$ unless scheduled for MVR
 - If not scheduled for MVR, left ventricular ejection fraction (LVEF) $\leq 35\%$ *** or
 - If LVEF $\leq 45\%$ and planned MVR
7. If not scheduled for MVR, New York Heart Association (NYHA) functional class III or IV
8. If scheduled for MVR, NYHA class II, III or IV
9. 6-minute walk test (6MWT) < 450 m
10. Serum glutamic oxaloacetic transaminase (SGOT/AST) and serum glutamic pyruvic transaminase (SGPT/ALT) $< 3x$ upper limit of normal
11. Acceptable pulmonary function by clinical assessment****
12. Available for follow-up
13. Signed informed consent

*Beta blocker not required for patients with mitral insufficiency

**Not required for patients with MV anomaly not likely to respond to medication and requiring surgical intervention

***May also be shown by cardiac catheterization, radionuclide scan, magnetic resonance imaging, and transthoracic echocardiogram

****If history of or current compromised pulmonary function, forced expiratory volume in 1 second (FEV₁) $> 50\%$ predicted normal value

2.3.2 Exclusion Criteria

Pre-enrollment testing occurred within one month prior to enrollment, unless otherwise specified, and was conducted after patients were stabilized on optimal medical therapy. Standard of care tests that were performed within the window for pre-enrollment testing but prior to signing a consent form were accepted as long as they met all of the protocol requirements.

Table 2
CorCap Study Exclusion Criteria

1. Planned cardiac surgery other than MVR*
2. Echocardiographic (or other) evidence of hypertrophic obstructive cardiomyopathy
3. Cardiomegaly estimated to exceed the largest available size of the CorCap device
4. Expectation that subject has cardiothoracic adhesions that would impair ability to gain complete, circumferential access to the heart
5. Any condition contraindicating extracorporeal circulation
6. Late-stage heart failure with increased surgical risk as defined by the presence of four or more of the following:
 - a. LVEDD \geq 80 mm
 - b. Peak $VO_2 \leq$ 13 ml/kg/min (cardiopulmonary exercise test)
 - c. Resting systolic BP \leq 80 mmHg (on clinical exam)
 - d. Atrial fibrillation (AF) at time of enrollment or paced rhythm with underlying AF
 - e. Heart failure duration \geq 8 years
 - f. Exercise-induced increase in systolic BP \leq 10% (cardiopulmonary exercise test)
 - g. 6-minute walk \leq 350 meters (1148 feet)
 - h. Previous cardiac surgery
 - i. BUN \geq 100 mg/dl
 - j. Cachexia (clinical impression)
7. Existing patent CABG or coronary artery disease sufficient for surgical revascularization**
8. On intraaortic balloon pump (IABP), intravenous inotropes or other vasoactive agents***
9. Currently needing (or anticipated need for) left ventricular assist device (LVAD) or other cardiac replacement device
10. On active heart transplant list or anticipated need for transplant within next 2 years
11. Acute myocardial infarction, unstable angina, or cerebral vascular accident (including transient ischemic attack) in past 3 months
12. Percutaneous coronary intervention or transmyocardial laser revascularization (TMR or PMR) within past 3 months
13. Presence of arrhythmias causing hemodynamic instability, history of resuscitated sudden death without subsequent treatment with implantable defibrillator or amiodarone, or AF with ventricular rate $>$ 100 bpm on meds
14. Co-morbid condition reducing life expectancy to $<$ 1 year
15. Serum creatinine \geq 3.5 mg/dl or dialysis dependent
16. Biventricular (BiV) pacing initiated in past 3 months or anticipated in next 12 months
17. Active infection
18. Pregnancy****
19. Enrolled in another investigational study that might confound interpretation of trial results
20. Unable to comply with protocol-required follow-up

*MVR could include tricuspid repair and/or atrial fibrillation ablation

**Subjects with a history of CAD who have not had an angiogram within the prior 3 years in whom revascularization has not been excluded should have repeat angiogram

***Immediate preoperative hemodynamic optimization with vasoactive agents, IABP, and IV inotropes OK

****Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior to randomization or must be using hormonal contraceptives or intrauterine device

2.3.3 Recruitment

Each clinical site had 3 key individuals directing study activities including a heart failure cardiologist, a heart failure CV surgeon and a study coordinator. There were 30 U.S. and one Canadian clinical centers that had undergone training in CorCap placement. Subjects were referred to cardiothoracic surgeon investigators by cardiology co-investigators. Baseline eligibility testing was conducted only after the subject was demonstrated to be on stable medical therapy.

2.4 Follow-Up Period

Subjects were followed according to the study's assessment schedule (see **Section 2.8**). The primary efficacy period ended with a common closing date of July 4, 2004, when the last patient enrolled had been followed for a minimum of one year. Patient follow up continues in the extended phase until each patient is followed for 5 years.

2.5 Pre-Enrollment Baseline Testing

Baseline assessments were performed in order to qualify patients and to document baseline functional and quality of life findings. Baseline assessments are listed in **Table 3**.

Table 3
Baseline Assessments

Test	Pre-enrollment
Clinical Assessment	X
Core Lab NYHA Assessment	X
Chest X-ray	X (within past 3 months)
Blood Tests	X
BNP	X
Echocardiography (transthoracic)	X
ECG	X (within past 3 months)
Cardiopulmonary Exercise Test	X (within past 3 months)
Six Minute Walk	X
MLHF and SF-36 Questionnaires	X
Right and/or Left Heart Catheterization	X*
<ul style="list-style-type: none"> • Information regarding vital status and adverse events were reported as they occurred. • Pre-enrollment testing was required within one month of enrollment except where noted and was completed after the patient was stabilized on optimal medical therapy. <p>*As required for patients with ischemic heart disease.</p>	

2.6 Randomization

Subjects meeting all inclusion and exclusion criteria were randomly assigned to treatment with CorCap or medical therapy. Randomization was stratified by whether or not subjects were planning to undergo MVR and by study center.

Separate randomization schedules were generated for each stratum (clinical site and MVR stratum). The randomization schedules were blocked. The first block in the randomization sequence was randomly chosen as a block of 2 or 4. All remaining blocks were blocks of 4.

The randomization schedules were produced in batches of 20. The sheets containing the randomization schedules were cut into individual strips, one assignment per strip. The strips were sealed within envelopes made of opaque colored paper. Envelopes were then labeled with the site number, stratum and patient accession number within the stratum. The envelopes remained sealed at Acorn until a patient was deemed eligible for the trial. No envelopes or other mechanisms for determining the randomization assignments were distributed to the sites.

Once patients were randomized, they were considered enrolled in the trial.

2.7 Study Procedure

The surgical procedure for treatment patients enrolled in the MVR stratum included implantation of the CorCap CSD after mitral valve surgery was performed. The surgical procedure for treatment patients enrolled in the No MVR stratum included implantation of the CorCap CSD only. The surgical procedure for control patients in the MVR stratum included mitral valve surgery only. Control patients in the No MVR stratum did not undergo surgery.

CorCap placement was performed according to the instructions for use and is summarized in **Table 4**. Investigators attempted to minimize the time between randomization and surgery for all patients requiring surgery. All surgeries (treatment and control) were performed a median of 8 days after randomization. All CorCap placements were performed by cardiothoracic surgeons who had undergone extensive training at Acorn.

Prior to study initiation, all centers received site and surgical training. All surgeons participating in the trial were required to participate in surgical training. Surgical training focused on the investigational plan, enrollment expectations and the surgical technique for CorCap CSD implantation. The cardiologist responsible for the study at each site attended either the site training or the surgical training.

Table 4
Summary of CorCap Placement Procedure

1. During surgery but prior to CorCap CSD implant, monitor cardiac geometry, function, and hemodynamic measurements to provide a baseline for acute post-implant comparisons.
2. Select CorCap CSD size based on intraoperative measurements performed at the time of surgery.
3. Custom fit the CorCap CSD to obtain a snug fit according to specific recommendations.
4. Secure the anterior seam of the device into the CorCap fitting clamp.
5. Trim the seam and excess fabric above the clamp.
6. Place a running suture below the jaws of the clamp to form a new anterior seam.
7. Perform a “tent test” on multiple locations on the heart.
8. Inspect the CorCap CSD and take additional LVEDD measurements via TEE.
9. Reinforce the new anterior seam with a second row of running suture to complete the procedure.

2.8 Follow-Up Assessment

For purposes of scheduling follow-up visits and measuring changes over time, “time zero” for patients undergoing surgery (either CorCap CSD implant or MVR) was the date of surgery. For patients not undergoing surgery, “time zero” was the date of enrollment (randomization).

All subjects were followed-up at 3, 6 and 12 months after enrollment. Follow-up also occurred yearly through year 5. Follow-up visits included assessments listed in **Table 5**.

Table 5
Follow-up Assessments

Test	Efficacy Phase: Follow-up at 3, 6, 12 , and every 6 months thereafter			Extended Follow-up Phase: Annually through the 5 year visit (+3 Mo.)
	3 Mo. (± 1 Mo.)	6 Mo. (± 1 Mo.)	12 Mo. & Every 6 Mo. (± 3 Mo.)	
Clinical Assessment	X	X	X	X
Core Lab NYHA Assessment		X	X	
Blood Tests	X	X	X	
BNP	X	X	X	
Echocardiography (transthoracic)	X	X	X	X
ECG	X	X	X Stop after 12 months	
Cardiopulmonary Exercise Test		X	X Stop after 12 months	
Six Minute Walk	X	X	X	
MLHF and SF-36 Questionnaires	X	X	X	
<ul style="list-style-type: none"> • Information regarding vital status and adverse events were reported as they occurred. • Follow-up testing was supplemented by regularly scheduled telephone assessment performed according to the following schedule: <ul style="list-style-type: none"> • Every 2 weeks through week 10 • Monthly between months 4 and 12 • Quarterly after month 12 (every 3 months) • Follow-up telephone assessments occur every 6 months during the extended follow-up phase <p>Telephone assessment was not required during intervals when the patient was seen for a follow-up visit.</p>				

In addition to visit-based follow-up, subjects were called by telephone every 2 weeks through week 10, monthly between months 4 and 12, and quarterly after month 12.

2.9 Adverse Events

Adverse events were reported continuously during follow-up. An adverse event was defined as any decrement in health status. A serious adverse event was defined as an adverse event that was:

- Life-threatening or resulted in death
- Required in-patient hospitalization or prolongation of hospitalization (in-patient stay of ≥ 24 hours)
- Resulted in permanent disability

Adverse events for conditions existing at baseline were reportable only if the condition worsened. Recurrent events that had previously resolved were reported as second occurrences. Reportable anticipated adverse events were defined in detail in the study protocol. All events were judged by site Investigators as to relatedness to the CorCap study device.

2.10 Other Study Mechanics

2.10.1 Clinical Events Review Committee

An independent Clinical Events Review Committee (CERC), consisting of 2 cardiologists and 1 cardiothoracic surgeon not otherwise involved with the study, reviewed submitted records for all study subjects in order to:

- Determine whether a subject experienced a major cardiac procedure performed because of progressive heart failure
- Review all serious adverse events (SAE), including death, and any other adverse events considered device-related
- Review adverse events where device relatedness could not be determined by the site
- Assess the relationship of serious adverse events to the device
- Review source documentation regarding each death that occurred during the trial
- Assess both attribution of death and underlying cause of death using a categorization scheme mutually developed by Acorn, the Data Safety Monitoring Board (DSMB), and CERC

Members of the CERC were not employees of Acorn, nor did they have any affiliation with the CorCap CSD randomized trial. All CERC members were blinded to treatment assignment for analysis of major cardiac procedures. CERC meetings were held biannually.

2.10.2 Medications

Subjects and their physicians were asked to maintain the same pharmacotherapy for heart failure as was used prior to study enrollment. **Table 6** summarizes the baseline

medications of the subjects enrolled in the trial. Compliance with this study directive was assessed by comparing medication usage as stated by the subject at post-enrollment visits with that used at the time of enrollment.

Table 6
Baseline Cardiac Medications

	# Patients	%
ACE or A II Blocker	291	97.0%
ACE Inhibitor	236	78.7%
Angiotensin II (A II) Blocker	70	23.3%
Beta Blocker	256	85.3%
Diuretic	294	98.0%

2.11 Endpoints

2.11.1 Primary Endpoint

The study's primary endpoint was a composite of death, the occurrence of one or more major cardiac procedures indicating progressive heart failure, and NYHA status as assessed by a central core lab upon review of information collected by blinded assessors at the study site. The composite endpoint at a minimum of one year was defined as listed in **Table 7**.

Table 7
Definitions for Composite Outcome Used for Primary Endpoint

Classification	Definition
Worse	Death <u>OR</u> major cardiac procedure <u>OR</u> increase by 1 or more NYHA class
Same	Alive <u>AND</u> no major cardiac procedure <u>AND</u> no change from baseline in NYHA class
Improved	Alive <u>AND</u> no major cardiac procedure <u>AND</u> decrease by 1 or more NYHA class

Major cardiac procedures included heart transplantation, implantation of cardiac assist or replacement device, CABG, implant of BiV pacing device,ⁱ subsequent MVR or tricuspid valve repair. Note that a major cardiac procedure counts towards the composite endpoint only if the procedure was performed, as assessed by the CERC, for progressive heart failure.ⁱⁱ

A composite approach was selected because: 1) expected morbidity and mortality in the recruited population is high and mortality was considered a “hard” objective endpoint; and 2) functional status, major cardiac procedures and death may be mutually exclusive outcomes. As an example, when a subject dies, functional status cannot be assessed. A subject may experience functional status improvement, but only after undergoing a major cardiac procedure, which, in most cases, is associated with a recovery period of poor overall health. Further, patients with progressive heart failure are commonly referred for additional treatments because of deteriorating signs and symptoms of heart failure. It was not ethical to withhold these treatments from patients in need and yet they were important milestones since they were indicated clinical deteriorations. The primary endpoint is useful statistically since it is ordered and uniquely determinable for each subject at each time point.

2.11.2 Secondary Endpoints

Secondary endpoints are listed in **Table 8** and included functional tests, structural (echocardiographic) and laboratory tests, and adverse events.

ⁱ Biventricular (BiV) pacing (also known as cardiac resynchronization therapy, CRT) was approved for the treatment of HF in 2001 during the study’s enrollment and follow-up period. BiV pacing is used to improve the electrical pacing of the heart and has been shown to improve quality of life in patients with HF. In this study, BiV pacing was considered a major cardiac intervention since it is typically performed for the treatment of unremitting symptoms of HF in patients who are candidates for the treatment (i.e., have appropriate prolonged QRS duration). Since BiV pacemaker placement is a relatively minor procedure compared to other cardiac procedures, and since BiV pacing is an elective – and therefore relatively discretionary – compared to other cardiac procedures, its use was counted as a major cardiac procedure only after a summary of indications for BiV pacing were reviewed by the study’s CERC, and the indication was deemed to be related to clear evidence of worsening heart failure.

ⁱⁱ VADs and heart transplantation were not adjudicated by the CERC; these were assumed to be caused by progressive heart failure.

Table 8
Secondary Endpoints by Endpoint Category*

<p><u>Functional</u></p> <ul style="list-style-type: none">• NYHA class from baseline to final follow-up (minimum of 12 months)• 6MWT• Quality of life as measured by SF-36 and MLHF questionnaires• Peak oxygen consumption, anaerobic threshold and exercise time <p><u>Structural (echocardiographic)</u></p> <ul style="list-style-type: none">• LVEDD, Left ventricular end systolic dimension (LVESD), Left ventricular ejection fraction (LVEF), LV end diastolic and systolic volumes (LVEDV and LVESV), mitral regurgitation, sphericity, pulmonary artery pressure and diastolic function <p><u>Laboratory</u></p> <ul style="list-style-type: none">• Peak oxygen consumption, anaerobic threshold and exercise time• B-type natriuretic peptide (BNP) <p><u>Adverse Events</u></p> <ul style="list-style-type: none">• All-cause mortality• All-cause rehospitalization• Major cardiac procedures

* All functional, echocardiographic and laboratory endpoints are a comparison of 12-month values to baseline.

2.12 Statistical Methods

Except as noted otherwise, all analyses were conducted under the intent-to-treat principle, in which subjects were assigned to their randomized groups regardless of the actual treatment received. All statistical tests were two-sided, with p-values of 0.05 or less defined as statistically significant. Statistical analysis was performed using SAS software versions 8.2 and 9.1 (SAS Institute, Cary, NC). Models included terms for stratification variables used in the study's randomization, including MVR vs. No MVR stratum and study site. Sites were grouped by level of enrollment as large (>16 subjects), medium (11-16 subjects), or small (<10 subjects) and these grouping categories were used in statistical analyses.

2.12.1 Imputing Missing Values

The primary endpoint for this trial was a clinical composite consisting of death, incidence of qualifying major cardiac procedures indicative of worsening heart failure, and change in blinded core lab NYHA classification from baseline to last follow-up visit. However, since the core-lab NYHA instrument was not implemented until enrollment was already underway due to ongoing negotiations with FDA, there were missing data in the blinded NYHA component at baseline. These data are therefore missing not because of patient

dropout or other potential causal relationships with outcomes, but simply because the blinded NYHA instrument had not been implemented until a number of patients had already been enrolled.

This resulted in the absence of a core lab-assessed NYHA at baseline for 174 patients, so statistical imputation was performed to estimate the baseline classification. As recommended by FDA, this was accomplished by the method of multiple imputation.¹¹ The advantage of multiple imputation was the preservation of valid statistical inference, by modeling the uncertainty in the process of estimating missing data.

Various other imputation methods (sensitivity analyses) with varying appropriate distributional assumptions and sufficiently broad sets of predictor variables, all support the conclusion that patients randomized to CorCap had significantly better clinical outcomes, as defined by the primary endpoint, than patients randomized to control. This supports the robustness of the multiple imputation method used. Lastly, an independent, blinded imputation was conducted by a third-party organization to validate the imputation procedures utilized in this study. The data were adequately validated.

2.12.2 Primary Endpoint

The primary composite endpoint placed patients into one of three categories: improved, same, or worsened. For this endpoint, deaths and major cardiac procedures were counted until the common closing date (July 4, 2004), which was defined to permit at least 12 months of follow-up for all enrolled patients. The change in core lab NYHA classification was calculated from the baseline to the patient's last visit prior to the common closing date.

2.12.3 Secondary Endpoints

Four secondary endpoints were considered "Major Secondary Endpoints." These four major secondary endpoints were selected *a priori* based on the primary function of the CorCap CSD and the goals of the clinical trial and included: left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), Minnesota Living with Heart Failure (MLHF) and site-assessed NYHA. To control for multiplicity, a pre-determined success criterion combining these four major secondary endpoints using the Hochberg's method¹² was defined a priori.

The major secondary endpoints were analyzed individually using repeated-measures methods which included main effects for randomization group and visit as well as their interaction, with the baseline of the outcome as a covariate.

Other secondary endpoints – those not deemed "major" secondary endpoints – were analyzed using appropriate statistical methods, including repeated-measures models, time-to-event methods including Kaplan-Meier and Cox regression methods, or categorical analyses as appropriate to the structure of the endpoint in question and the timing of its collection during study follow-up.

2.12.4 Justification for Pooling

The justification for pooling of the MVR and No MVR strata is based on the clinical hypothesis that the direction of the benefit related to the CorCap CSD would be the same. Poolability across strata was tested statistically by several criteria and found to be appropriate.

2.12.5 Study Power

The study's sample size of 300 patients (150 per group) was based on requiring 90% power to detect odds of being classified as "improved at 12 months compared to baseline" at least twice as great in the CorCap CSD group as in the pharmacotherapy alone group with a two-sided alpha of 0.05. Alternative power calculations using 1) a continuous-type approach (assigning scores of -1, 0 and 1 to the study's primary endpoint categories) and 2) a Wilcoxon rank statistic approach resulted in similar sample sizes. The likelihood of subjects being classified as improved was taken from other published randomized trials of subjects with heart failure. The sample size also took into account a 5% missing data rate. Although randomization was stratified by planned MVR, the study was not powered to detect significant differences in the individual strata; nor was it powered to detect significant differences in the individual components of the primary composite endpoint.

2.13 Methods to Reduce Study Bias

Since this trial had to be conducted in an unblinded fashion, several design features were implemented to reduce the potential for bias:

1. Four core labs blinded to treatment allocation were established to review endpoint data: echocardiography, BNP, exercise, and NYHA.
2. An independent CERC reviewed and adjudicated all major cardiac procedures (MCP) blinded to treatment status.
3. An independent DSMB, chaired by Dr. Gary Francis, was formed to oversee the conduct of the trial. The DSMB had the authority to terminate the trial if there was evidence of an adverse effect. They could not terminate the trial if there was early evidence of increased efficacy.
4. Acorn and the investigators were kept blinded to the aggregate results.

3.0 CLINICAL STUDY RESULTS

3.1 Study Sites

Table 9 lists sites (30 U.S. and 1 Canadian) and physicians participating in this study as of December 17, 2004.

Table 9
Physicians at Study Sites Enrolling Subjects

Name of Center (Site ID)	Surgeon Investigators	Cardiology Investigators
Advocate Christ Hospital / University of ILL at Chicago Chicago, IL (3050 CHI)	Mark Slaughter, MD	Marc Silver, MD
Albert Einstein/Montefiore New York, NY (3750 AECM)	Margarita Camacho	Thierry LeJemtel, MD
Baylor College of Medicine Houston, TX (3550 BAY)	Ernesto Soltero, MD	Doug Mann, MD Biykem Bozkurt, MD Suzanne Sorof, MD
Boston Medical Center Boston, MA (4800 BMC)	Richard Shemin, MD Oz M. Shapira, MD Harold Lazar, MD	Wilson Colucci, MD George Philippides, MD
BryanLGH Medical Center / BryanLGH Heart Institute Lincoln, NE (4700 LGH)	Edward Raines, MD	Steve Krueger, MD
Cedars-Sinai Medical Center Los Angeles, CA (4300 CSMC)	Alfredo Trento, MD	Steven Khan, MD
Cleveland Clinic Foundation Cleveland, OH (3500 CCF)	Nicholas Smedira, MD Patrick McCarthy, MD	Randall Starling, MD James Young, MD
Columbia-Presbyterian Medical Center New York, NY (3100 CPMC)	Yoshifumi Naka, MD, PhD Surgeon co-Investigator has disclosable financial interests; see FDA Form 3455 for Memhet Oz, MD	Donna Mancini, MD
Duke University Medical Center Durham, NC (4200 Duke)	Carmelo Milano, MD	Stuart Russel
Henry Ford Hospital Detroit, MI (3800 HFH)	Robert Brewer, MD	Barbara Czerska, MD

Name of Center (Site ID)	Surgeon Investigators	Cardiology Investigators
Hospital of the University of Pennsylvania / Presbyterian Hospital Philadelphia, PA (3300 HUP)	Principal surgeon investigator has disclosable financial interests; see FDA Form 3455 for Michael Acker, MD	Mariell Jessup, MD
McGill University / Royal Victoria Hospital Montreal, Canada (4000 MONT)	Renzo Cecere, MD	Nadia Giannetti, MD
Nebraska Heart Institute Lincoln, NE (3700 NHI)	James Wudel, MD	Kaliprasad Ayala, MD
Newark Beth Israel Hospital Newark, NJ (4900 NBI)	Daniel J. Goldstein, MD	Mark J. Zucker, MD Hillel Ribner, MD Luis Arroyo, MD
New England Medical Center Hospital / Tufts Univ Boston, MA (4250 NEMC)	Kamal Khabbaz, MD	David DeNofrio, MD Marvin Konstam, MD
North Shore Long Island University Hospital Manhasset, NY (4350 NSLI)	Margarita Camacho, MD Alan Hartmann, MD	Hal Skopicki, MD
Oschner Heart & Vascular Institute New Orleans, LA (3450 OCH)	Cliff VanMeter, MD	Mandeep Mehra, MD Robert Scott, MD Myung Park, MD
Penn State College of Medicine - Milton H. Hershey Medical Center Hershey, PA (3150 HERS)	Walter Pae, MD Sanjay Mehta, MD	John Boehmer, MD David Silber, MD
St. Louis University Medical Center St Louis, MO (4400 SLUH)	Alan Ahoran	Paul Hauptman, MD
Stanford University Medical Center / Kaiser Permanente Stanford, CA (3650 STAN)	Robert Robbins, MD Bruce Reitz, MD	Michael Fowler, MD Dana Weisshaar, MD
Temple University Hospital Philadelphia, PA (4500 TUH)	Satoshi Furukawa, MD Mahender Macha, MD James McChurken, MD Arun Singhal, MD	Howard Eisen, MD Gail Berman, MD Shelley Hankins, MD Paul Mather, MD Kenneth Marguiles, MD Sharon Rubin, MD Joyce Wald, MD

Name of Center (Site ID)	Surgeon Investigators	Cardiology Investigators
Univ of Florida/Shands Gainesville, FL (3250 UFL)	Edward Staples, MD Thomas Beaver, MD	Juan Aranda, MD
University of Alabama at Birmingham Birmingham, AL (3600 UAB)	James Kirklin, MD David McGriffin, MD	Barry Rayburn, MD
University of Louisville at Jewish Hospital Louisville, KY (3900 JHL)	Rob Dowling, MD	Geetha Bhat, MD
University of Maryland Baltimore, MD (4150 UMD)	James Gammie, MD Bartley Griffith, MD Robert Poston, MD James Brown, MD	Stephen Gottlieb, MD Shawn Robinson, MD
University of Michigan Hospitals Ann Arbor, MI (3200 MICH)	Steven F. Bolling, MD Francis D. Pagani, MD	Keith D. Aaronson, MD David S. Bach, MD David B Dyke, MD Ragavendra Baliga, MD
University of Minnesota Minneapolis, MN (4600 Uof M)	Soon Park	Leslie Miller, MD
University of Pittsburgh Medical Center Pittsburgh, PA (3950 PITT)	Kenneth McCurry, MD Guy Gowan, MD Robert Kormos, MD Michael Mathier, MD	Srinivas Murali, MD Pittsburgh, PA 15213 Dennis McNamara, MD Michael Feldman, MD
VA Medical Center Minneapolis Minneapolis, MN (4100 VAMN)	Herbert Ward, MD	Inder Anand, MD
VA Medical Center San Diego Health Care System San Diego, CA (3350 VASD)	Michael Madani, MD	Ralph Shabetai, MD Alan Maisel, MD (stepped down as PI; will serve as co- investigator)
Washington Hospital Center Washington, DC (3400 WHC)	Ammar Bafi, MD Cardiac Surgery	Brian D. Carlos, MD

3.2 Subject Enrollment by Site

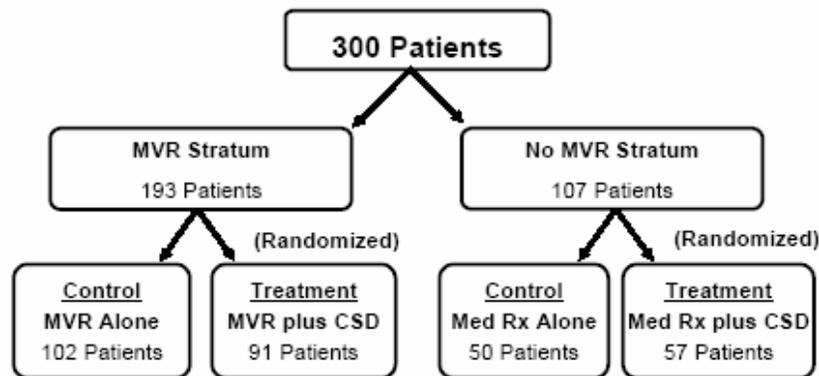
300 subjects were enrolled at 29 study sites. Enrollment by study site and whether MVR was planned at enrollment is shown in **Table 10**.

Table 10
Study Enrollment by Site and MVR Stratum

Site ID	Site Name	Number of Subjects		
		MVR	No MVR	Total
3050	Christ Hospital	8	1	9
3100	Columbia Presbyterian	11	-	11
3150	Hershey Medical Center	1	8	9
3200	University of Michigan	21	1	22
3250	University of Florida	-	18	18
3300	University of Pennsylvania	27	1	28
3350	VA San Diego	-	1	1
3400	Washington Hospital Center	9	7	16
3450	Ochsner Clinic	2	1	3
3500	Cleveland Clinic Foundation	9	6	15
3550	Baylor Methodist VA	2	4	6
3600	University of Alabama	10	6	16
3650	Stanford University/Kaiser Permanente	9	1	10
3700	Nebraska Heart Institute	15	5	21
3750	Albert Einstein Medical Center	9	-	9
3800	Henry Ford Hospital	6	10	16
3900	Jewish Hospital	2	12	14
3950	University of Pittsburgh	3	-	3
4000	McGill University	5	5	10
4100	VA Minnesota	-	2	2
4150	University of Maryland	1	3	4
4200	Duke University	5	2	7
4250	New England Medical Center	-	1	1
4300	Cedars Sinai Medical Center	3	-	3
4350	North Shore Long Island	-	-	0
4400	St. Louis University	6	5	11
4500	Temple University	-	-	0
4600	University of Minnesota	2	-	2
4700	Bryan LGH Hospital	23	5	27
4800	Boston Medical Center	-	2	2
4900	Newark Beth Israel	4	-	4
Total	-	193	107	300

Of the 300 subjects, 193 were scheduled for MVR and 107 were not. Of the subjects scheduled for MVR, 102 were assigned to MVR alone and 91 were assigned to MVR plus CorCap placement (**Figure 1**). All subjects received appropriate medical therapy for heart failure. Of the subjects not scheduled for MVR, 50 were assigned to medical treatment alone and 57 were assigned to medical treatment plus CorCap.

Figure 1
Subject Assignment by MVR Treatment Stratum*



* Randomization was stratified by whether MVR was scheduled at baseline.

3.3 Baseline Characteristics

Baseline characteristics of subjects stratified by whether MVR was planned at baseline are shown in **Table 11**. In general, subjects planning to undergo MVR were older and had more prominent echocardiographic findings.

Overall, the distribution of baseline clinical, physical examination, laboratory and echocardiographic characteristics was similar across the CorCap treatment groups. However, there were statistically significant differences between groups for gender and peak VO₂, with the treatment (CorCap) group having a higher percentage of females (53.4% vs. 36.2%; p=0.001) and a lower peak VO₂ (13.8 vs. 15.5 ml/kg/min; p=0.0005) than the control group. Additionally, the CorCap group had a lower diastolic blood pressure (DBP) that was nearly significant (68.9 vs. 71.5 mmHg; p=0.053); this reached statistical significance (p=0.044) in the MVR Stratum.

Because of the statistically significant differences and clinical relevance of gender, peak VO₂, and DBP, adjustments for baseline imbalances were performed. All analyses of the primary endpoint in this report utilize covariate adjustment of the baseline imbalances observed for gender, peak VO₂, and DBP.

Table 11
Baseline Characteristics of Subjects Stratified by Whether MVR was Planned at Baseline

	MVR Planned		MVR Not Planned		Total		
	CorCap (n=91)	No CorCap (n=102)	CorCap (n=57)	No CorCap (n=50)	CorCap (n=148)	No CorCap (n=152)	All (n=300)
Age, mean (SD)	54.1 (13.3)	52.8 (12.0)	51.8 (11.8)	49.7 (12.0)	53.2 (12.8)	51.7 (12.0)	52.5 (12.4)
Female, n (%)	59 (64.8)	46 (45.1)	20 (35.1)	9 (18.0)	79 (53.4)	55 (36.2)	134 (44.7)
Race, n (%)							
White	57 (62.6)	59 (57.8)	43 (75.4)	36 (72.0)	100 (67.6)	95 (62.5)	195 (65.0)
Black	28 (30.8)	31 (30.4)	12 (21.1)	10 (20.0)	40 (27.0)	41 (27.0)	81 (27.0)
Other	6 (6.6)	12 (11.8)	2 (3.5)	4 (8.0)	8 (5.4)	16 (10.5)	24 (8.0)
Heart Failure Etiology, n (%)*							
Valvular	16 (17.6)	17 (16.7)	0 (0.0)	1 (2.0)	16 (10.8)	18 (11.8)	34 (11.3)
Ischemic	6 (6.6)	6 (5.9)	10 (17.5)	8 (16.0)	16 (10.8)	14 (9.2)	30 (10.0)
Idiopathic	52 (57.1)	65 (63.7)	36 (63.2)	31 (62.0)	88 (59.5)	96 (63.2)	184 (61.3)
Viral	6 (6.6)	6 (5.9)	6 (10.5)	7 (14.0)	12 (8.1)	13 (8.6)	25 (8.3)
Alcoholic	1 (1.1)	2 (2.2)	2 (3.5)	1 (2.0)	3 (2.0)	3 (2.0)	6 (2.0)
Hypertensive	10 (11.0)	10 (9.8)	7 (12.3)	3 (6.0)	17 (11.5)	13 (8.6)	30 (10.0)
Other	8 (8.8)	9 (8.8)	3 (5.3)	5 (10.0)	11 (7.4)	14 (9.2)	25 (8.3)
Years since heart failure diagnosis, mean (SD)	4.1 (3.8)	5.2 (4.3)	5.1 (4.0)	5.7 (4.8)	4.5 (3.9)	5.4 (4.4)	5.0 (4.2)
Clinical history, n (%)							
Hypertension	44 (48.4)	50 (49.0)	29 (50.9)	27 (54.0)	73 (49.3)	77 (50.7)	150 (50.0)
Angina	12 (13.3)	16 (15.7)	13 (22.8)	6 (12.0)	25 (17.0)	22 (14.5)	47 (15.7)
Coronary artery disease	10 (11.0)	10 (9.8)	11 (19.3)	9 (18.0)	21 (14.2)	19 (12.5)	40 (13.3)
Myocardial infarction	9 (9.9)	11 (10.8)	10 (17.5)	6 (12.0)	19 (12.8)	17 (11.2)	36 (12.0)
Permanent pacemaker	11 (12.1)	16 (15.7)	11 (19.3)	9 (18.0)	22 (14.9)	25 (16.4)	47 (15.7)
ICD	18 (19.8)	25 (24.5)	15 (26.3)	11 (22.0)	33 (22.3)	36 (23.7)	69 (23.0)
Cardiac surgery	1 (1.1)	3 (2.9)	0 (0.0)	1 (2.0)	1 (0.7)	4 (2.6)	5 (1.7)
COPD	10 (11.0)	15 (14.7)	3 (5.3)	2 (4.0)	13 (8.8)	17 (11.2)	30 (10.0)
Diabetes	24 (26.4)	19 (18.6)	21 (36.8)	18 (36.0)	45 (30.4)	37 (24.3)	82 (27.3)
Renal dysfunction	2 (2.2)	4 (3.9)	1 (1.8)	1 (2.0)	3 (2.0)	5 (3.3)	8 (2.7)

	MVR Planned		MVR Not Planned		Total		
	CorCap (n=91)	No CorCap (n=102)	CorCap (n=57)	No CorCap (n=50)	CorCap (n=148)	No CorCap (n=152)	All (n=300)
Atrial Fibrillation	16 (17.6)	28 (27.5)	9 (15.8)	6 (12.0)	25 (16.9)	34 (22.4)	59 (19.7)
Other Arrhythmia	26 (28.6)	41 (40.2)	24 (42.1)	21 (42.0)	50 (33.8)	62 (40.8)	112 (37.3)
Bi-Ventricular Pacemaker	5 (5.5)	5 (4.9)	3 (5.3)	5 (10.0)	8 (5.4)	10 (6.6)	18 (6.0)
Cardiac Arrest	1 (1.1)	2 (2.0)	2 (3.5)	2 (4.0)	3 (2.0)	4 (2.6)	7 (2.3)
Number of prior HF hospitalizations, mean (SD)	1.1 (1.2)	1.0 (1.2)	0.8 (1.2)	1.1 (1.6)	1.0 (1.2)	1.1 (1.3)	1.0 (1.3)
Physical examination, mean (SD)							
SBP (mm Hg)	109.2 (17.8)	112.9 (18.0)	110.0 (17.0)	110.9 (14.6)	109.5 (17.4)	112.2 (16.9)	110.9 (17.2)
DBP (mm Hg)	68.0 (11.3)	71.8 (13.9)	70.2 (11.4)	71.0 (9.5)	68.9 (11.4)	71.5 (12.6)	70.2 (12.1)
Heart Rate (bpm)	77.0 (15.1)	77.5 (14.0)	75.2 (14.70)	77.0 (15.3)	76.3 (14.9)	77.3 (14.4)	76.8 (14.6)
Medication use, n (%)							
ACE Inhibitor	73 (80.2)	84 (82.4)	46 (80.7)	33 (66.0)	119 (80.4)	117 (77.0)	236 (78.7)
AII Blocker	21 (23.1)	19 (18.6)	12 (21.1)	18 (36.0)	33 (22.3)	37 (24.3)	70 (23.3)
Any ACE or AII Blocker	88 (96.7)	100 (98.0)	55 (96.5)	48 (96.0)	143 (96.6)	148 (97.4)	291(97.0)
Beta blocker	75 (82.4)	80 (78.4)	54 (94.7)	47 (94.0)	129 (87.2)	127 (83.6)	256 (85.3)
Diuretic	90 (98.9)	97 (95.1)	57 (100.0)	50 (100.0)	147 (99.3)	147 (96.7)	294 (98.0)
Echocardiographic findings, mean (SD)							
LVESD (mm)	61.2 (11.6)	63.2 (11.5)	63.5 (10.8)	63.0 (11.4)	62.1 (11.3)	63.1 (11.4)	62.6 (11.3)
LVEDD (mm)	71.2 (10.3)	72.4 (9.7)	72.5 (10.2)	72.6 (11.3)	71.7 (10.2)	72.5 (10.2)	72.1 (10.2)
LVEDDi (mm/m ²)	35.8 (5.9)	36.5 (6.2)	34.9 (5.1)	34.0 (5.4)	35.5 (5.7)	35.7 (6.1)	35.6 (5.8)
LV volume (ml)	266.6 (99.3)	273.3 (101.7)	278.9 (121.9)	285.6 (134.6)	271.2 (108.1)	277.1 (112.7)	274.2 (110.3)
LVEF (%)	27.8 (10.4)	28.2 (9.0)	25.0 (6.8)	27.0 (7.5)	26.8 (9.2)	27.8 (8.6)	27.3 (8.9)
Pulmonary artery pressure (mm Hg)	43.7 (14.2)	42.2 (14.4)	33.6 (9.9)	38.7 (15.7)	40.8 (13.8)	41.6 (14.6)	41.1 (14.1)
Diastolic Dysfunction, n (%)	16 (21.1)	16 (18.4)	19 (35.8)	13 (28.3)	35 (27.1)	29 (21.8)	64 (24.4)
Relaxation Abnormalities	28 (36.8)	35 (40.2)	9 (17.0)	13 (28.3)	37 (28.7)	48 (36.1)	85 (32.4)
Restrictive physiology	20 (26.3)	24 (27.6)	22 (41.5)	14 (30.4)	42 (32.6)	38 (28.6)	80 (30.5)
Pseudonormal physiology	12 (15.8)	12 (13.8)	3 (5.7)	6 (13.0)	15 (11.6)	18 (13.5)	33 (12.6)
Unable to evaluate							

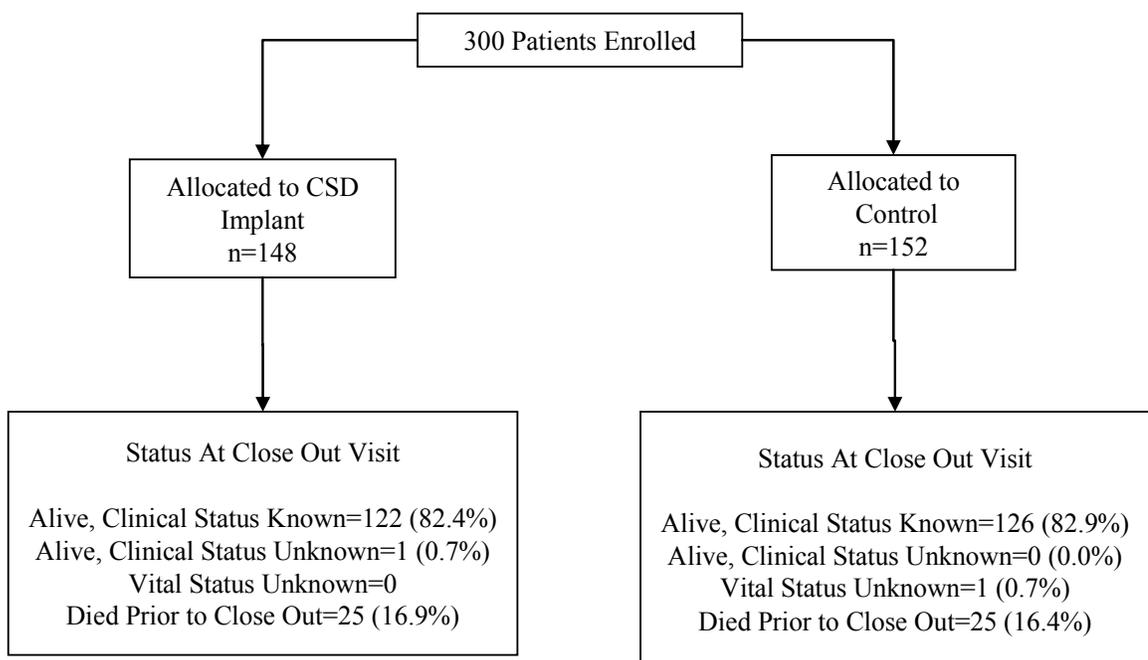
	MVR Planned		MVR Not Planned		Total		
	CorCap (n=91)	No CorCap (n=102)	CorCap (n=57)	No CorCap (n=50)	CorCap (n=148)	No CorCap (n=152)	All (n=300)
Quality of life score, mean (SD)							
MLHF score	57.4 (24.1)	60.1 (23.7)	65.9 (15.9)	59.7 (22.5)	60.6 (21.7)	60.0 (23.2)	60.3 (22.4)
SF-36: Physical Function	35.8 (22.6)	38.3 (23.2)	32.4 (18.8)	34.4 (23.1)	34.4 (21.3)	37.0 (23.1)	35.8 (22.2)
SF-36: General Health	35.4 (20.5)	38.0 (21.7)	29.8 (17.9)	33.1 (16.7)	33.3 (19.7)	36.4 (20.3)	34.9 (20.0)
Functional tests, mean (SD)							
Peak VO2 (ml/kg/min)	13.3 (4.1)	14.8 (4.4)	14.7 (3.4)	16.8 (4.7)	13.8 (3.9)	15.5 (4.6)	14.7 (4.3)
6-Minute Walk Distance (meters)	346.0 (79.1)	342.8 (100.0)	329.4 (82.4)	340.6 (76.6)	339.6 (80.5)	342.1 (92.6)	340.9 (86.7)
Functional status, n (%)							
Site-assessed NYHA Class I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Class II	22 (24.2)	23 (22.5)	0 (0.0)	0 (0.0)	22 (14.9)	23 (15.1)	45 (15.0)
Class III	66 (72.5)	72 (70.6)	56 (98.2)	50 (100.0)	122 (82.4)	122 (80.3)	244 (81.3)
Class IV	3 (3.3)	7 (6.9)	1 (1.8)	0 (0.0)	4 (2.7)	7 (4.6)	11 (3.7)
Core-lab assessed** NYHA							
Class I	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.8)
Class II	3 (8.6)	3 (6.7)	1 (3.8)	1 (5.0)	4 (6.6)	4 (6.2)	8 (6.3)
Class III	13 (37.1)	24 (53.3)	11 (42.3)	8 (40.0)	24 (39.3)	32 (49.2)	56 (44.4)
Class IV	19 (54.3)	17 (37.8)	14 (53.8)	11 (55.0)	33 (54.1)	28 (43.1)	61 (48.4)
Laboratory tests, mean (SD)							
BNP (median, pg/ml)	116.0	111.0	67.0	30.9	79.0	85.0	85.0
BUN (mg/dl)	24.1 (11.9)	22.7 (12.3)	21.9 (11.1)	21.9 (10.5)	23.3 (11.6)	22.4 (11.7)	22.8 (11.6)
Creatinine (mg/dl)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)
Sodium (mEq)	138.6 (3.4)	138.5 (3.3)	138.8 (3.8)	138.4 (3.2)	138.7 (3.5)	138.5 (3.3)	138.6 (3.4)
Hemoglobin (g/dl)	13.3 (1.5)	13.4 (1.7)	13.5 (1.5)	14.0 (1.5)	13.4 (1.5)	13.6 (1.7)	13.5 (1.6)

Abbreviations: LV: left ventricular; LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end diastolic diameter; LVEDDi: left ventricular end diastolic diameter index. *Patients can have multiple etiologies **Only 126 patients had a core lab NYHA at baseline.

3.4 Subject Flow Chart

Figure 2 shows the flow of subjects through the study. Of the 148 subjects assigned to CorCap treatment, 139 underwent CorCap placement and 9 did not. Reasons for non-receipt of the assigned surgical treatment include refusing surgery (n=7) or death prior to surgery (n=2). These 9 subjects were included in subsequent analyses up to the point of study withdrawal or death in an intent-to-treat approach. No patient in whom MVR was not planned initially underwent the procedure (some underwent MVR placement in follow-up, see below).

Figure 2
Subject Flow in Study



3.5 Visit Attendance

Compliance with study visits was excellent, with 90% of subjects attending required visits if they remained alive.

Table 12
Compliance with Study Visits

Follow-Up Visit (mo)	CorCap			No CorCap			Total		
	Theo	Act	%	Theo	Act	%	Theo	Act	%
3	139	132	95.0	145	128	88.3	284	260	91.5
6	134	125	93.3	141	121	85.8	275	246	89.5
12	130	123	94.6	129	116	89.9	259	239	92.3
18	82	79	96.3	85	74	87.1	167	153	91.6
24	60	56	93.3	51	44	86.3	111	100	90.1
30	27	22	81.5	24	18	75.0	51	40	78.4
36	10	10	100.0	9	5	55.6	19	15	78.9
42	5	5	100.0	3	2	66.7	8	7	87.5
48	2	1	50.0	0	-	-	2	1	50.0
All Visits	589	553	93.9	587	508	86.5	1176	1061	90.2

Theo = theoretically available (i.e., not dead); Act = actually attended visit.

3.6 Surgery Results

Table 13 summarizes clinical characteristics of subjects undergoing cardiothoracic surgery with or without MVR and CorCap placement. The median time from randomization to surgery was 8 days.

Table 13
Characteristics of Initial Surgical Procedure in Study Participants

Clinical Characteristic	MVR Planned				MVR Not Planned			
	CorCap		No CorCap		CorCap		No CorCap*	
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
Total anesthesia time (hrs)	87	4.9 (1.7 – 9.7)	95	4.5 (1.5 – 8.9)	51	3.7 (1.6 – 8.9)	-	-
Skin-to-skin time (hrs)	87	3.5 (1.5 – 6.8)	93	3.1 (1.2 – 7.2)	51	2.0 (0.8 – 6.4)	-	-
CP bypass time, if used (min)	87	99 (35 – 205)	97	85 (30 – 217)	10	25 (10-98)	-	-
Crossclamp time, if used (min)	87	56 (19-132)	96	59 (20-185)	-	-	-	-
Post-op length of hospitalization (days)	87	9 (4-110)	97	7 (2-114)	52	7 (1-34)	-	-
Post-op ICU length of stay (days)	87	4 (0-48)	97	2 (1-54)	52	3 (1-24)	-	-
Duration on post-op ventilator (hrs)	84	12 (1-1080)	97	10 (1-936)	52	5 (0-312)	-	-

* Subjects did not undergo surgery

Cardiopulmonary bypass was used in all subjects who had MVR. Only 19.2% (10/52) of subjects who underwent CorCap placement alone required cardiopulmonary bypass. In the CorCap subjects alone, median time of bypass (25 minutes) was shorter than that typically provided during MVR (median 85 minutes).

Table 14 summarizes patient disposition for all patients who were randomized into the study.

Table 14
Patient Disposition

	MVR Stratum (N = 193) n (%)			No MVR Stratum (N = 107) n (%)			Total (N = 300) n (%)		
	No CorCap MVR Alone 102 (52.85)	CorCap MVR plus CSD 91 (47.15)	Total	No CorCap Med Rx Alone 50 (46.73)	CorCap Med Rx plus CSD 57 (53.27)	Total	No CorCap 152 (50.67)	CorCap 148 (41.33)	Total
Compliant (received CorCap surgery)									
n (%)	n/a	88 (97%)		n/a	51 (89%)		n/a	139 (94%)	
Not Compliant (did not receive CorCap)									
n (%)	n/a	3 (3%)		n/a	6 (11%)		n/a	9 (6%)	
Mortality (Date Of Surgery)									
<= 30 days (peri-operative)	1 (1%)	2 (2%)	3	0 (0%)	5* (9%)	5	1 (1%)	7* (5%)	8
30 days < n ≤ 6 months	7 (7%)	5** (5%)	12	2 (4%)	1 (2%)	3	9 (6%)	6** (4%)	15
6 months < n ≤ 12 months	7 (7%)	4 (4%)	11	4 (8%)	2 (4%)	6	11 (7%)	6 (4%)	17
12 months < n ≤ 24 months	1 (1%)	1 (1%)	2	2 (4%)	2** (4%)	4	3 (2%)	3** (2%)	6
24 months < n	1 (1%)	3 (3%)	4	0 (0%)	0 (0%)	0	1 (1%)	3 (2%)	4
Mortality (Date Of Randomization)									
<= 30 days	1 (1%)	0 (0%)	1	0 (0%)	5* (9%)	5	1 (1%)	5* (3%)	6
30 days < n ≤ 6 months	7 (7%)	6** (6%)	13	2 (4%)	1 (2%)	3	9 (6%)	7** (5%)	16
6 months < n ≤ 12 months	7 (7%)	5 (5%)	12	4 (8%)	2 (4%)	6	11 (7%)	7 (5%)	18
12 months < n ≤ 24 months	1 (1%)	1 (1%)	2	2 (4%)	2** (4%)	4	3 (2%)	3** (2%)	6
24 months < n	1 (1%)	3 (3%)	4	0 (0%)	0 (0%)	0	1 (1%)	3 (2%)	4
Completed Follow-Up									
<= 30 days	1 (1%)	2 (2%)	3	0 (0%)	5 (9%)	5	1 (1%)	7 (5%)	8
30 days < n ≤ 6 months	7 (7%)	5 (5%)	12	2 (4%)	1 (2%)	3	9 (6%)	6 (4%)	15

	MVR Stratum (N = 193) n (%)			No MVR Stratum (N = 107) n (%)			Total (N = 300) n (%)		
	No CorCap MVR Alone 102 (52.85)	CorCap MVR plus CSD 91 (47.15)	Total	No CorCap Med Rx Alone 50 (46.73)	CorCap Med Rx plus CSD 57 (53.27)	Total	No CorCap 152 (50.67)	CorCap 148 (41.33)	Total
6 months < n ≤ 12 months	6 (6%)	4 (4%)	10	4 (8%)	2 (4%)	6	10 (7%)	6 (4%)	16
12 months < n ≤ 24 months	47 (46%)	42 (46%)	89	23 (46%)	23 (40%)	46	70 (46%)	65 (44%)	135
24 months < n	31 (30%)	36 (40%)	67	14 (28%)	22 (39%)	36	45 (30%)	58 (39%)	103
Lost to Follow-Up / Withdrew									
<= 30 days	1 (1%)	1 (1%)	2	0 (0%)	1 (2%)	1	1 (1%)	2 (1%)	3
30 days < n ≤ 6 months	2 (2%)	0 (0%)	2	3 (6%)	2 (4%)	5	5 (3%)	2 (1%)	7
6 months < n ≤ 12 months	3 (3%)	0 (0%)	3	2 (4%)	1 (2%)	3	5 (3%)	1 (1%)	6
12 months < n ≤ 24 months	3 (3%)	0 (0%)	3	1 (2%)	0 (0%)	1	4 (3%)	0 (0%)	4
24 months < n	1 (1%)	1 (1%)	2	1 (2%)	0 (0%)	1	2 (1%)	1 (1%)	3

N = number of patients

n = number of patients in each arm

% = n / N x 100%

* Includes one patient who died the day of her enrollment and randomization (9 June 2003) which was prior to having surgery to place the CorCap device

** Includes one pt. in each cell who did not receive CorCap despite randomization assignment

3.7 Primary Composite Endpoint

The primary endpoint of the study was a composite outcome taking into account death, the occurrence of a major cardiac procedure (MCP) associated with worsening heart failure and functional status as classified by NYHA class. As shown in **Table 15**, amongst all randomized subjects, the distribution of clinical outcomes favored the CorCap group compared to the control. When considering patients in separate strata by whether MVR was planned, the trend towards improvement was significant in the No MVR stratum but not statistically significant in the MVR stratum. It is noted that the study was not powered to detect an incremental benefit of the CorCap over MVR surgery alone.

Table 15
Primary Study Outcome by MVR Stratum

Outcome Status, n (%)	MVR Planned		No MVR Planned		All Subjects	
	CorCap (n=91)	No CorCap (n=102)	CorCap (n=57)	No CorCap (n=50)	CorCap (n=148)	No CorCap (n=152)
Improved	39.6	31.3	34.7	19.3	37.7	27.3
Same	23.6	25.7	27.4	31.6	25.1	27.7
Worsened	36.8	43.0	37.9	49.1	37.2	45.1
Odds Ratio	1.51		2.57		1.73	
P-value*	0.17		0.032		0.024	

* P-values derived from a proportional-odds model including MVR stratum, size of clinical site, duration of follow-up and baseline covariates.

3.7.1 Components of Primary Endpoint

As mentioned previously, the study was not powered to test for statistical differences between groups of individual components of the primary composite variables. However, trends in these variables were examined for exploratory purposes. Analyses were conducted for individual components of the primary composite endpoints:

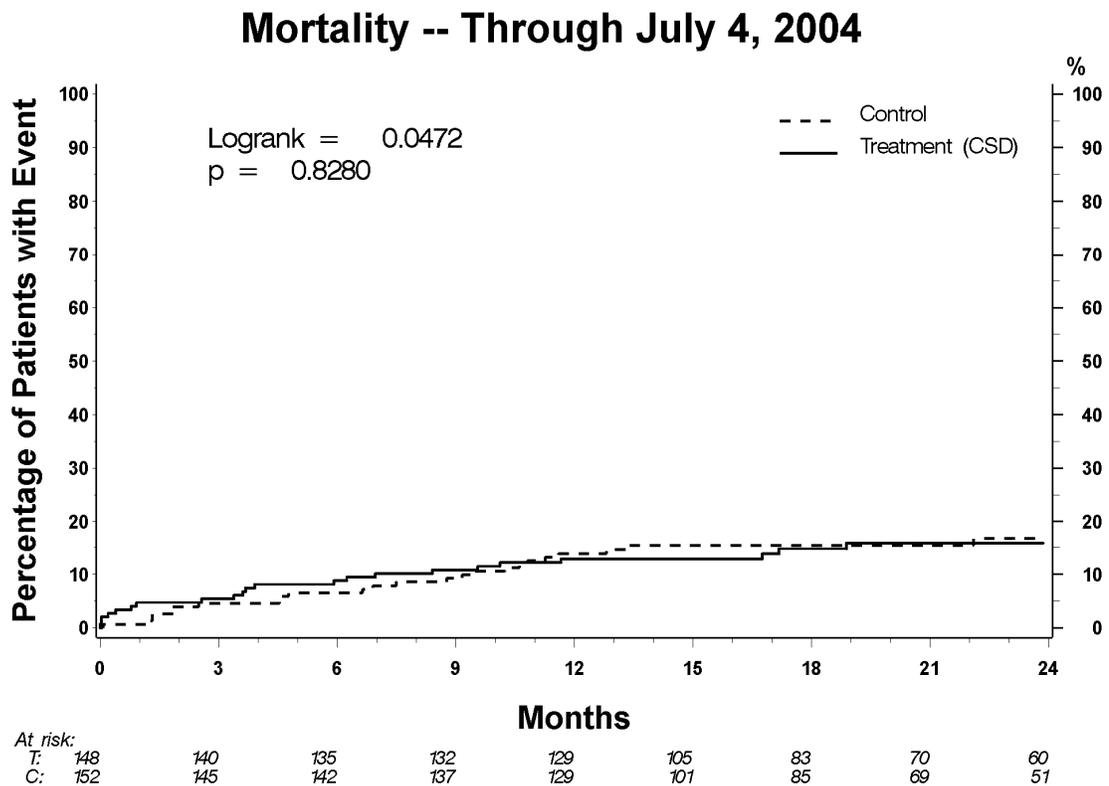
- Death
- Incidence of major cardiac procedures indicative of worsening heart failure
- Change in core-lab NYHA from baseline to final follow-up

These components are summarized below. Analyses of survival incidence of major cardiac procedures for heart failure were performed using time-to-event methods, and thus appropriately censor subjects. The analysis of change in NYHA classification is a proportional-odds model analogous to that used in the primary endpoint as a whole.

3.7.2 Primary Endpoint Component: Mortality

Time from enrollment (no CorCap group) or CorCap placement to death, study withdrawal or end of the study was noted for each subject. **Figure 3** shows subject mortality vs. time by treatment group. Overall, there were 25 deaths in each of the control and treatment groups. A Kaplan-Meier analysis shows no differences in overall survival (p=0.83). Mortality results were updated on 30 December 2005, yielding 38 deaths in control and 32 deaths in treatment (p=0.52).

Figure 3
Mortality in CorCap Study (Original PMA Data)



Similar to the main analysis, no statistically significant difference in survival occurred up to 24-months within the MVR and No MVR strata. A higher number of perioperative deaths occurred in the CorCap group amongst subjects not undergoing MVR in comparison to the control group not undergoing surgery. These events are described in **Section 3.9.1**.

3.7.3 Primary Endpoint Component: Major Cardiac Procedures

The second component of the primary endpoint was incidence of major cardiac procedures. In total, major cardiac procedures occurred in 19 patients (with a total of 21 procedures) in the CorCap group and in 33 patients (with a total of 48 procedures) in the control group (p=0.01). Compared to the control group, the treatment group had fewer patients with cardiac transplants (7 versus 16) and LVAD implants (3 versus 8).

A total of 41 major cardiac procedures during the follow-up period required review by the CERC. LVADs and heart transplants were not adjudicated, but assumed to be heart failure related. Of these, 32 were deemed to be associated with worsening heart failure by the CERC. **Figure 4** shows the Kaplan Meier curve of freedom from a major cardiac procedure; fewer patients experienced a major cardiac procedure in the CorCap group compared to control (p=0.009). An analysis of individual major cardiac procedure types (**Table 16**) summarizes the incidences of major cardiac procedures in the treatment and control groups; fewer CorCap patients experienced each type of major cardiac procedure compared to the control.

In the No MVR group, there were 5 procedures in 5 patients (1 transplant) in the treatment group, compared to 16 procedures in 12 patients in the control group (which included 6 transplants), which was a significant difference (p = 0.02). In the MVR group, there were 16 procedures in 14 patients in the treatment group, compared to 32 procedures in 21 patients in the control group.

Figure 4
Subject Survival Free from Major Cardiac Procedure by Treatment Group

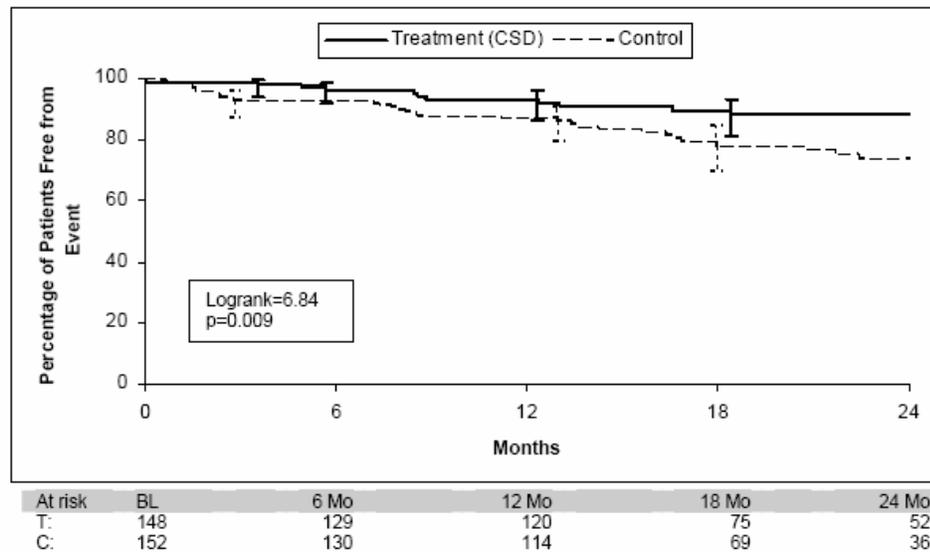


Table 16
Subjects Who Had a Major Cardiac Procedure During Follow-up Period

Event	CorCap (n=148)	No CorCap (n=152)	HR (T/C) (95% CI)*	p-value
Cardiac Transplant	7	16	0.42 (0.17-1.02)	0.06
LVAD	3	8	0.40 (0.11-1.51)	0.18
MVR**	1	3	NA	NA
Bi-Ventricular Pacing	10	14	0.60 (0.26-1.41)	0.24
TVR	0	2	NA	NA
Any of above procedures***	19	33	0.46 (0.25-0.83)	0.01

*Hazard ratio of time to first MCP computed by Cox proportional hazards model

**MVR in follow-up (doesn't count planned initial MVR in subjects in the MVR stratum)

***Subjects may have had more than one event

Table 17
Subjects Who Had a Major Cardiac Procedure During Follow-up Period by MVR Stratum

Event	MVR Planned				MVR Not Planned			
	CorCap (n=91)	No CorCap (n=102)	HR*	p-value	CorCap (n=57)	No CorCap (n=50)	HR*	p-value
Cardiac Transplant	6	10	0.63 (0.23, 1.74)	0.37	1	6	0.13 (0.01, 1.06)	0.06
LVAD	3	6	0.57 (0.14, 2.28)	0.43	0	2	NA	NA
MVR**	1	3	NA	NA	0	0	NA	NA
Bi-Ventricular Pacing	6	7	0.75 (0.24, 2.36)	0.62	4	7	0.47 (0.13, 1.67)	0.24
TVR	0	2	NA	NA	0	0	NA	NA
Any of above procedures***	14	21	0.57 (0.28, 1.16)	0.12	5	12	0.28 (0.09, 0.88)	0.03

*Hazard ratio computed by Cox proportional hazards model

**MVR in follow-up (doesn't count planned initial MVR in subjects in the MVR stratum)

***Subjects may have had more than one event

3.7.4 Primary Endpoint Component: Functional Status (NYHA)

The third component of the primary endpoint was functional status as assessed by NYHA classification, assessed by a central core laboratory. At final follow-up, outcomes were better in the CorCap group than in the control, but the difference was not statistically

significant (**Table 18**). Note that subjects who had died or had undergone a major cardiac procedure were censored from the analysis.

Table 18
Functional Status Improvement by Treatment and MVR Stratum

Change from baseline in NYHA Status (% of patients)	MVR Planned		No MVR Planned		All Subjects	
	CorCap (n=91)	No CorCap (n=102)	CorCap (n=57)	No CorCap (n=50)	CorCap (n=148)	No CorCap (n=152)
Improved	55.7	48.2	47.1	31.5	52.3	42.8
Same	33.2	39.6	37.2	51.6	34.8	43.4
Worsened	11.2	12.2	15.7	16.9	13.0	13.8
Odds ratio* (p-value)	1.45 (0.35)		2.37 (0.16)		1.64 (0.12)	

* P-values derived from a proportional-odds model including MVR stratum, size of clinical site, duration of follow-up and baseline covariates.

3.8 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints for the study are listed in **Table 19**. Subsequent sections describe results for each test.

Table 19
Secondary Effectiveness Endpoints

Test Category	Tests
Functional	NYHA, 6-Minute Walk Test, Peak oxygen consumption, anaerobic threshold and exercise time
Quality of Life	SF-36 (GHD), SF-36 (PFD), MLHF
Structural (Echocardiographic)	LVEDD, LVESD, LVEF, LVEDV, LVESV, cardiac sphericity, LV mass
Laboratory	B-type natriuretic peptide (BNP)

3.8.1 Secondary Effectiveness: Functional Outcomes

This section describes secondary effectiveness outcomes for functional endpoints.

NYHA Status

Changes in core-lab NYHA status – a component of the primary composite endpoint – was described in **Section 3.7.4**. There was no significant difference between treatment and control in site-assessed NYHA. (p=0.60).

6-Minute Walk Test

6-minute walk test (6MWT) distance was to be measured at baseline and follow-up. However, a substantial number of subjects did not undergo 6MWT. The most common reasons for missing tests listed on the case report forms included “too sick,” “currently in hospital,” or “too symptomatic.” In total, 6MWT was performed in 78% of CorCap subjects and 66% of No CorCap subjects. Thus, there were large amounts of missing data and tests were missing for cause (more missing tests in control patients who tended to be sicker). This made interpretation of test results difficult. To account for the missing test, a rank order analysis was done. This resulted in an odds ratio of 1.27 favoring the treatment group, although this change was not statistically significant (p=0.24).

Cardiopulmonary Exercise Testing (CPX test)

Similar to the 6 minute walk test, a substantial number of subjects did not undergo cardiopulmonary exercise testing. In total, CPX testing was performed in 74% of treatment patients and only 62% of control patients. Again, these exercise tests were missing for cause; the most common reasons for missing tests included “too sick,” “currently in hospital,” or “too symptomatic.” Further, patients who were missing follow-up exercise tests were “sicker,” as evidenced by lower a baseline peak VO₂, shorter 6 minute walk distance, and worsened MLHF scores compared to patients who completed follow-up exercise tests. This made interpretation of test results difficult. To account for the missing test, a rank order analysis was done. This resulted in an odds ratio of 1.37 favoring the treatment group, although this change was not statistically significant (p=0.15).

3.8.2 Secondary Effectiveness: Quality of Life Outcomes

MLHF

At baseline and each follow-up visit, subjects self-rated quality of life with the Minnesota Living With Heart Failure (MLHF) questionnaire. Both CorCap and No CorCap subjects showed decreases in mean MLHF questionnaire scores (**Figure 5**), but the CorCap group showed a larger improvement in score (p = 0.04 by repeated measures analysis). The improvement in MLHF scores was about 16 points in subjects treated with CorCap and 12 points in subjects treated without CorCap (**Table 20**).

Figure 5
Change in MLHF Questionnaire Score by Treatment Group and Follow-up Time

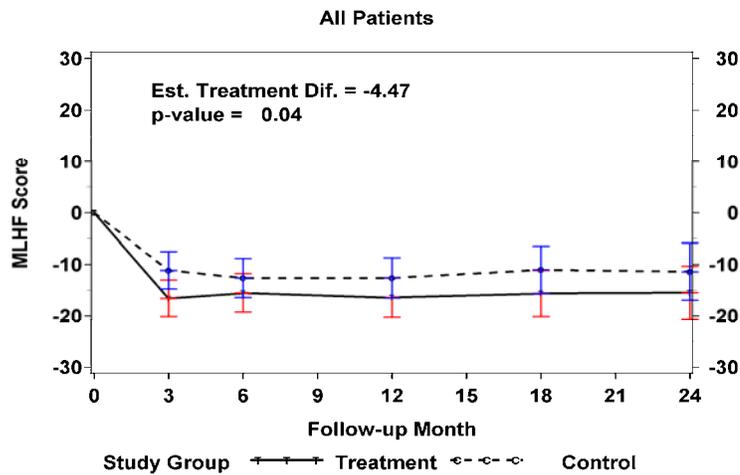


Table 20
Change in MLHF Questionnaire Score from Baseline by Treatment and Study Visit

Study Visit	CorCap		No CorCap	
	N*	Mean Change (95% CI)	N	Mean Change (95% CI)
3 Mo	133	-16.6 (-20.1, -13.0)	127	-11.1 (-14.7, -7.5)
6 Mo	128	-15.5 (-19.3, -11.8)	122	-12.6 (-16.4, -8.8)
12 Mo	125	-16.4 (-20.2, -12.6)	119	-12.6 (-16.5, -8.7)
18 Mo	79	-15.6 (-20.1, -11.2)	73	-11.1 (-15.6, -6.5)
24 Mo	56	-15.5 (-20.6, -10.4)	47	-11.4 (-16.9, -5.9)

*MLHF scores were not available in all subjects due to death and study withdrawal

SF-36

SF-36, a generic quality of life instrument used in over 4000 clinical trials,¹³ was assessed at baseline and all follow-up visits.

General Health Domain. Subjects treated with both CorCap and No CorCap showed improvements in the GH domain, but the increase in GH scores was approximately 9 points larger for subjects treated with CorCap ($p < 0.0001$ by repeated measures analysis, (Table 21, Figure 6).

Figure 6
Change in SF-36 General Health Domain by Study Treatment and Follow-up Visit

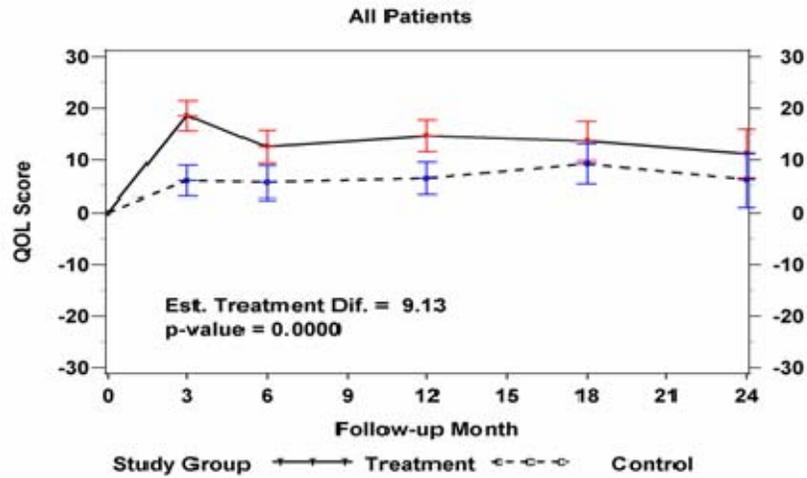


Table 21
Improvement from Baseline in General Health Domain of SF-36 by Treatment Group and Study Visit

Study Visit	CorCap		No CorCap	
	N	Mean Change (95% CI)	N	Mean Change (95% CI)
3 Months	133	18.5 (15.5, 21.4)	127	6.0 (3.0, 9.0)
6 Months	128	12.5 (9.3, 15.7)	122	5.7 (2.4, 8.9)
12 Months	125	14.6 (11.5, 17.7)	119	6.4 (3.2, 9.6)
18 Months	79	13.6 (9.8, 17.4)	74	9.2 (5.3, 13.1)
24 Months	56	11.2 (6.4, 15.9)	47	6.2 (1.1, 11.2)

Physical Function domain. The physical function (PF) domain of SF-36 improved in both group but the improvement in subjects treated with CorCap was approximately 5.4 points greater (p = 0.015, repeated measures analysis, **Table 22**).

Figure 7
Improvement from Baseline in Physical Function Domain of SF-36 by Treatment Group and Study Visit

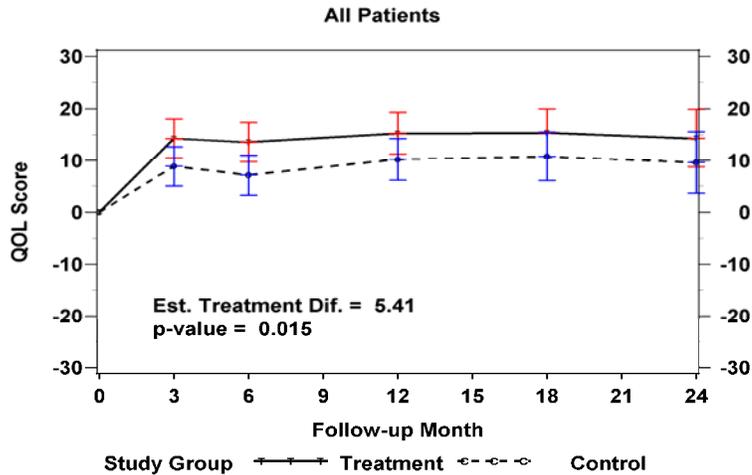


Table 22
Improvement from Baseline in Physical Function Domain of SF-36 by Treatment Group and Study Visit

Study Visit	CorCap		No CorCap	
	N	Mean Change (95% CI)	N	Mean Change (95% CI)
3 Months	132	14.3 (10.5, 18.0)	126	8.9 (5.1, 12.7)
6 Months	128	13.6 (9.8, 17.4)	122	7.2 (3.3, 11.0)
12 Months	124	15.2 (11.2, 19.3)	119	10.2 (6.1, 14.3)
18 Months	79	15.4 (10.8, 20.0)	74	10.8 (6.1, 15.5)
24 Months	56	14.3 (8.8, 19.9)	47	9.6 (3.7, 15.6)

3.8.3 Secondary Effectiveness: Structural Measurements

Secondary effectiveness endpoints included several structural (echocardiographic) measurements. **Table 23** shows changes in structural measurements at 12 months compared to baseline. Except for LVEF, all measurements show statistically significant improvements in structural parameters or trends towards improvement.

Table 23
12-Month Change From Baseline in Structural (Echocardiographic) Measurements

12-month change from baseline, mean (95% CI)	CorCap		No CorCap		P-value for difference***
	N	Mean	N	Mean	
LVEF, %	97	3.7 (1.4, 6.0)	88	0.2 (-2.2, 2.6)	0.49
LV end systolic volume, ml	97	-25.9 (-37.9, -13.9)	88	-8.2 (-20.8, 4.4)	0.02
LV end diastolic volume, ml	97	-32.7 (-45.4, -20.0)	88	-17.2 (-30.5, -3.9)	0.008
Cardiac sphericity index*	97	0.10 (0.07, 0.14)	87	0.03 (0.00, 0.07)	0.031
Left ventricular mass, g**	97	-14.9 (-23.9, -5.9)	88	-13.6 (-22.2, -4.9)	0.15
Left ventricular end diastolic dimension, mm	89	-5.8 (-7.4, -4.3)	79	-3.6 (-5.1, -2.0)	0.02
Left ventricular end systolic dimension, mm	87	-4.8 (-6.8, -2.9)	79	-2.5 (-4.5, -0.5)	0.21

*Ratio of left ventricular length to left ventricular width, both measured at end diastole. A normal cardiac sphericity index is approximately 1.58.

** $LVMass(g) = 1.04 \times [(LVEDD + PWT + IVST)^3 - LVEDD^3] \times 0.8 + 0.6$

***Based on repeated measures ANOVA using multiple measurements in follow-up

3.8.4 Secondary Effectiveness: Other Measurements

BNP

The CorCap group had higher BNP levels and a rise in BNP levels compared to the No CorCap group, which showed decreased BNP levels (p=0.014 for group differences by repeated measures analysis). This hypothesis was difficult to test in the present study because over 55% of patients had a normal (i.e., less than 100 pg/ml) level of BNP at baseline. Further, an article published by Packer indicates that additional study is needed to define the role of routine BNP measurements in the diagnosis and management of chronic heart failure, and that evidence to date suggests that levels of BNP should not be viewed as a diagnostic test for chronic heart failure. In addition, he indicates that sequential measurements in patients with established heart failure have not been shown to be useful in assisting in the follow-up of patients or in the initiation or titration of appropriate medications.¹⁴ This finding was reported in a study by Tang et al. from the Cleveland Clinic. Similar to our study, Tang et al demonstrated that 25% of patients referred to the Cleveland Clinic have normal BNP levels despite advanced HF. Thus, it is difficult to use BNP as a measurement of efficacy or therapeutic interventions.¹⁵

All-Cause Re-hospitalizations

The number of times a subject was hospitalized during the year of follow-up was recorded. The distribution of rehospitalizations did not differ between treatment groups (p=0.44, Van Elteren’s test).

All-Cause Mortality or Re-hospitalization

The combination endpoint of death or re-hospitalization was listed as a secondary endpoint. **Table 24** demonstrates that there were no differences between the treatment and control groups in this combination endpoint.

Table 24
Death or Re-Hospitalization

	Treatment (n=148)		Control (n=152)		HR (T/C) (95% C.I.)	p-value
	# Pts	Rate*	# Pts	Rate*		
Death or Re-hospitalization	111	7.6	111	7.6	1.02 (0.78, 1.33)	0.88

*rates/100 patient months

3.9 Safety Endpoints

3.9.1 Perioperative Deaths

The perioperative period was defined as the day of surgery (CorCap placement with or without prior MVR) to 30 days after surgery. Within the perioperative period, 6 subjects died in the CorCap group and 1 subject died in the No CorCap group. Causes of death amongst these subjects are described in **Table 25**. An additional patient died on the day of enrollment (prior to CorCap placement) and there fore is not included in the table. No common cause of death was observed. By 12 months, the likelihood of death was similar in both treatment groups.

Table 25
Summaries of Perioperative Deaths

Number	Patient ID	Treatment	Cause of Death
1	3904	CorCap	Nine-days post-operatively the patient had recovered, however, the patient was noted to have multiple runs of asymptomatic non-sustained ventricular tachycardia post operatively. The patient was reluctant to take amiodarone due to previous side effects. Due to the patient's poor prognosis and inability to tolerate hemofiltration, the spouse decided to stop life support measures. Twelve days after surgery, the patient died. Cause of Death Reported by Site: Multisystem Organ Failure /Ventricular Arrhythmia.
2	3153	CorCap	History of CAD. Experienced several episodes of hypotension and had sudden cardiac death 1 day after surgery. Cause of Death Reported by Site: Ventricular Arrhythmia.
3	3807	CorCap	Progressive multiorgan failure and died 24 days after surgery. Cause of Death Reported by Site: Multi-Organ Failure/Sepsis.
4	4407	CorCap	Prolonged anesthesia during CorCap implant procedure due to Swan-Ganz catheter placement delay. Repeat surgery for post-op bleeding followed by multiple episodes of ventricular tachycardia. Subject died one day after surgery. Cause of Death Reported by Site: Post-Operative Bleeding.
5	3453	CorCap + MVR	Subject had tenuous cardiovascular status preoperatively and postoperative SVT with hypotension, AF, ventricular arrhythmias and bacteremia. Cardiac arrest and death occurred 6 days after surgery. Cause of Death Reported by Site: Cardiogenic Shock.
6	4405	CorCap + MVR	Prolonged (10 hours) anesthesia. Postoperative AF, kidney failure with dialysis, AF, sternal dehiscence and gastric tear with peritonitis (unrelated to CorCap placement). Subject died 28 days after surgery due to sepsis. Cause of Death Reported by Site: Sepsis.
7	3308	MVR	Postoperative coagulopathy, hypotension due to low cardiac output, multiple episodes of ventricular arrhythmias refractory to amiodarone and lidocaine, stroke. Eventually, life support was withdrawn and the subject died 2 days after surgery. Cause of Death Reported by Site: Cardiogenic Shock

3.10 Clinical Evidence of Constrictive Physiology

There was no clinical indication from either follow-up or adverse event forms of constrictive physiology at any time during the study. In addition to this strong evidence of safety, Acorn has committed to continued monitoring of the IDE cohort patients for evidence of constrictive physiology for 5 years. FDA has agreed that, given the nature of pericardial constriction, it is more appropriate to monitor for constrictive physiology in the post-market setting.¹⁶

3.11 Other Adverse Events

Table 26 shows the number of subjects with serious adverse event (SAE) by treatment group. Overall, 78% of patients in the control group and 81% of patients in the treatment group experienced at least 1 serious adverse event in follow-up. The proportion of subjects experiencing each type of SAE did not differ across treatment groups. No device-related adverse events occurred during the study.

Table 26
Adverse Events by AE Type and Treatment (Original PMA Data)

	Any Serious Adverse Event				
	CorCap (n=148)		No CorCap (n=152)		p-value
	N	%	N	%	
Allergic Response	3	2.0	1	0.7	0.22
Arrhythmia	48	32.4	58	38.2	0.39
Bleeding	9	6.1	14	9.2	0.33
Hemodynamic Compromise	83	56.1	73	48.0	0.18
Hepatic Compromise	2	1.4	0	0.0	0.14
Infection/Pneumonia	46	31.1	35	23.0	0.08
Myocardial Infarction	1	0.7	2	1.3	0.56
Neurological Deficit/Stroke	16	10.8	11	7.2	0.23
Peripheral Thrombus/Embolism	3	2.0	3	2.0	0.96
Pulmonary Compromise	29	19.6	22	14.5	0.17
Pulmonary Embolism	2	1.4	1	0.7	0.57
Renal Compromise	15	10.1	8	5.3	0.12
Other	59	39.9	58	38.2	0.74
Any SAE	120	81.1	118	77.6	0.43

*P-value based on Cochran-Mantel-Haenzel test

Each entry represents the number of subjects who experienced an AE.

The number of SAEs was updated on April 15, 2005. The total number of patients that experienced a serious adverse event was not statistically different between the treatment and control groups. At this time point, 83.1% of the CorCap group experienced any serious adverse event compared to 78.9% of the control group. Of the 13 SAE categories, only one showed a significant difference between treatment and control; specifically, hemodynamic compromise, which favored control (p=0.04). Analysis of hemodynamic compromise by Cox regression showed that only early events (within 30 days after surgery) in the No MVR stratum were significantly different.

3.12 Additional Results

3.12.1 Focused Cohort Results

In response to the FDA's August 12, 2005 not approvable letter providing three options to render the PMA approvable, Acorn chose to reanalyze the pivotal trial data using *post hoc* analyses that excluded high risk patients in order to establish a patient population in which the risk-benefit profile was improved.

This proposed patient segmentation which used LVEDD indexed by body mass index (iLVEDD), was clinically validated by outside reviewers and investigators. The results of this per-protocol analysis demonstrate a more favorable risk-benefit profile in a Focused Cohort of patients. The Focused Cohort consists of 159 patients whose LVEDDi is greater than or equal to 30 mm/m² and less than or equal to 40 mm/m².

The primary composite endpoint was achieved with an odds ratio of 2.45 (p=0.011). The CorCap CSD treatment group had a greater frequency of "improved" compared to the control group (42.5% vs. 26.6%). The odds ratio and p-value in the Focused Cohort were better than the odds ratio (OR=1.73) and p-value (p=0.024) in the original 300 patient cohort, which was consistent with the intent of the post hoc subgroup analysis. All 3 components of the primary endpoint (mortality, major cardiac procedures and change in NYHA class) moved in the same direction. The treatment group in the Focused Cohort experienced 34% fewer deaths (p=0.17), a significant reduction in MCPs (p=0.013) and favorable results in NYHA class (p=0.18).

There were no significant differences between the treatment and control groups in terms of the number of patients with an SAE (81.8% vs. 78.0%; p=0.88) or the Kaplan-Meier time to event analysis for the combination of death or SAE (p=0.79). The CorCap CSD perioperative mortality rate was 1.3% (1/77), indicating no excess surgical risk for treatment.

An additional safety and efficacy measure was the endpoint of heart failure-related hospitalizations. The Kaplan-Meier curve for time to death or first heart failure-related hospitalization indicated a statistically significant treatment effect (p=0.042).

4.0 ADDITIONAL SAFETY DATA

4.1 EU Marketing Experience

The CorCap CSD received CE Marking for concomitant use in September of 2000 and for CorCap CSD only use in April of 2001. As of 29 September 2006, a total of 277 CorCap CSDs have been implanted in patients from seven European countries including France, Germany, Netherlands, Sweden, Belgium, Italy, and Great Britain. The CorCap CSD has not been removed from the market in any country for reasons related to the safety and effectiveness of the device. To date, two customer complaints have been filed. One was related to a patient adverse event that was determined to be not-device related, and the other was a product-related comment unrelated to any adverse event. Two adverse events (in one patient) were prospectively reported under the EU randomized trial and were classified as “possibly device-related” by the investigator. None of these complaints or adverse events met the criteria for Vigilance Reporting; thus, no Vigilance Reports have been filed for the CorCap CSD.

5.0 RISK/BENEFIT ANALYSIS

5.1 Benefits

This randomized controlled trial has provided sufficient evidence to show that treatment of patients with dilated cardiomyopathy and systolic heart failure with implantation of the CorCap CSD is both safe and effective. Effectiveness was shown by demonstrating that subjects assigned to treatment with CorCap showed improved outcome status as measured by the study's composite primary endpoint. This endpoint, which combined NYHA functional status, incidence of adjudicated major cardiac procedures and death, was significantly better in the CorCap group vs. the No CorCap group. When expressed as odds ratios, the CorCap group had a 73% better odds of being in improved functional status group compared to the No CorCap group. Additionally, the clinical study results are consistent with preclinical studies.

The likelihood of favorable clinical outcomes was statistically higher for the study overall; the trend towards favorable outcomes was apparent in both the MVR and No MVR strata. The primary endpoint was supported by numerous secondary echocardiographic and quality of life endpoints showing that CorCap treatment was associated with improved cardiac function. Secondary endpoint success criteria were significantly improved for SF-36 and all the structural measurements except LVEF.

Weighing in favor of the benefits of the CorCap CSD is the lack of other treatments in subjects with end-stage heart failure due to systolic dysfunction. All enrolled subjects were on optimal medical therapy throughout the study, including diuretics, ACE inhibitors or equivalent, and beta blockers. Other than very invasive treatments (LVAD, transplant) or prolonged intravenous therapy, no other options are currently available.

5.2 Risks

Any implanted cardiac device carries risk. In addition, the population in which CorCap is used is one of high expected short-term mortality due to underlying severe cardiac dysfunction. Nonetheless, the following points were demonstrated in the clinical study:

- The risk of death during follow-up did not differ between subjects assigned to CorCap vs. those assigned to treatment without CorCap.
- The rate of serious adverse events did not differ between the CorCap and No CorCap groups.
- CorCap CSD placement resulted in a decrease in the rate of major cardiac procedures for heart failure.

6.0 SAFETY QUESTIONS RAISED BY FDA

FDA had three safety concerns regarding the CorCap CSD, as presented in the August 12, 2005 not-approvable letter for the PMA and in subsequent discussions with Acorn. This section reviews and responds to these questions with extensive safety data based on the clinical trial results, including the focused cohort analysis, and independent expert reviews.

6.1 Perioperative Deaths

FDA expressed concern regarding the risk of death within the first 30 days after surgery. The rate of perioperative death by cohort and strata is listed below in **Table 27**.

Table 27
Perioperative Mortality in the 300-Patient and Focused Cohort, By Strata

	Both Strata		MVR Strata		No MVR Strata	
	CorCap CSD	No CorCap	CorCap CSD	No CorCap	CorCap CSD	No CorCap
300-Patient Cohort	6/139 (4.3%)	1/102 (1.0%)	2/88 (2.3%)	1/102 (1.0%)	4/51 (7.8%)	N/A
Focused Cohort	1/77 (1.3%)	1/57 (1.8%)	0/46 (0.0%)	1/57 (1.8%)	1/31 (3.2%)	N/A

6.1.1 Pivotal Trial

In the pivotal trial, there were 7 perioperative deaths. Six (6) of these deaths occurred in individuals randomized to the CorCap CSD group (6/139 or 4.3%) and 1 occurred in the control group. For the group of patients randomized to CorCap CSD treatment, 1 patient died prior to CorCap CSD implant surgery and 9 patients who were randomized did not undergo implant surgery. Thus, the actual perioperative death rate was 6/139 (4.3%). This rate was consistent with published databases for patients undergoing mitral valve replacement (3.12%¹⁷ to 8.17%¹⁸) and mitral valve repair (1.37%¹⁹ to 4.28%²⁰). By 12 months, there was no increased risk of the CorCap CSD.

Additionally, a surgical learning curve appears to have affected the rate of mortality and this variable can be controlled by improved training and instruction. In 2001, there were 2 deaths after 12 surgeries (16.7%). In 2002, after 20 more implants, there were two deaths (10.0%). At this time, surgeons were retrained with the recommendation to use IABP and cardiopulmonary bypass during the surgeries. By 2003, there were 19 more implants and zero deaths. With this experience and improved instructions for use, a greater level of safety due to improved surgical implantation can be expected.

6.1.2 Focused Cohort

The Focused Cohort analysis sought to address FDA's concerns by identifying a subset of patients with an improved risk-benefit ratio. In the Focused Cohort of 159 patients with an LVEDDi ≥ 30 and ≤ 40 mm/m², there was an overall reduction in mortality by 34% (overall mortality rates of 21/82 [25.6%] patients in the control group and 13/77 [16.9%] in the CorCap CSD group). For the 30-day time period, there was only 1 death in the treatment group and 1 death in the control group. Thus, the LVEDDi criterion for implantation of the CorCap CSD effectively identified a patient population at reduced perioperative implant risk. A 3.2% rate of mortality falls within what is commonly accepted for cardiac surgery.

6.2 Adhesions

FDA also expressed concern that the CorCap device leads to an excessive number of adhesions on the heart, which could negatively impact future re-operations. Specifically, at the Panel meeting on June 22, 2005, an operative report by Dr. Patrick McCarthy was quoted during discussion of this issue in a context that may have been misleading. His response to concerns that dense adhesions due to the CorCap could adversely affect re-operation is found in an **Attachment**.

In re-operations that took place after 30 days (i.e., cardiac transplantation), adhesions were reported in 100% of CorCap CSD patients and 70% of the control group. Dense adhesions can occur after CorCap CSD placement, but they can occur following *any* cardiac surgery. Even though there were adhesions in all CorCap CSD re-operation patients, all the follow-on procedures were performed safely with good outcomes, including transplantation. Of the 7 CorCap patients and 16 control patients who received transplants, AEs per patient were virtually the same (1.7 in CorCap group and 1.9 in control group) and the post-operative stay was shorter for the CorCap group (12.3 versus 19.6 days). Additionally, a group of independent experts was convened to discuss re-operations. They made significant recommendations to patient management practice that were incorporated into the product labeling and training.

6.3 Long-Term Constriction

There was no indication from either follow-up or adverse event forms of constrictive physiology at any time during the study. In addition to this strong evidence of safety, Acorn has committed to continued monitoring of the IDE cohort patients for evidence of constrictive physiology for 5 years. FDA has agreed that, given the nature of pericardial constriction, it is more appropriate to monitor for constrictive physiology in the post-market setting.²¹

7.0 CONCLUSIONS

The results of this study demonstrate the safety and effectiveness of the CorCap CSD in patients with heart failure due to systolic dysfunction. The CorCap CSD pivotal study was a multi-center, prospective, stratified and randomized, controlled evaluation of 300 patients with heart failure and constituted one of the largest controlled studies involving a permanent device implant and cardiac surgery in patients with heart failure. The trial met the protocol-specified criteria for success and demonstrated significant clinical benefits, and an acceptable safety profile. Results from a supplemental analysis to optimize the patient population (i.e., the Focused Cohort), conducted in response to an FDA not approvable letter, demonstrate an improved benefit-risk profile, and augment the original trial results.

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ATTACHMENT
LETTER FROM DR. PATRICK McCARTHY

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NORTHWESTERN
UNIVERSITY

August 4, 2005

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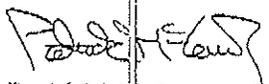
Dear Ms. Fleischer:

I am writing to you regarding the recent panel discussion of the Acorn device. One of my operative reports was read at the panel, in the context that the Acorn device poses considerable risks to patients because of the formation of dense adhesions. I was not present at the panel, but this information came back to me from three different sources, and many people thought that my letter was read out of context.

In my operative report, I mentioned that dense adhesions had formed around the Acorn device to the pericardium. Surgeons encounter dense adhesions at re-operations, especially during LVAD explants, while waiting for a donor heart. This was placed in the operative report: 1) to note that this occurred so other investigators, and other surgeons, would know to be aware that this takes a considerable amount of time to remove the device (as well as the heart) in preparation for transplant, 2) there are implications regarding the feasibility of performing coronary artery bypass or other surgery, once an Acorn device has been placed. However, I was surprised and disappointed at the vote of the panel. I had already contacted Acorn about using their device here at Northwestern. I think that it serves a useful role in a select group of patients. There are no other commercially available devices, or surgical procedures, that address advanced heart failure in this patient population without the need for transplantation or expensive cardiac assist devices.

When I heard about the report of the panel I contacted Spencer Kubo from Acorn to express my disappointment, and surprise that my operative report was partially read, and certainly out of context. Dr. Kubo suggested that I should write to you about these concerns and to clarify my feelings about the Acorn device. I hope that you will take this into consideration during your review of the device. Please do not hesitate to contact me if you should have any questions.

Sincerely yours,


Patrick M. McCarthy, MD
PMM/lf

The Joseph and Bessie Feinberg Foundation is endowed by Bernard, Louis, Rouben, and Samuel H. Feinberg
The McGraw Medical Center of Northwestern University