

# **I. SUMMARY OF SAFETY AND EFFECTIVENESS**

## **A. General Information**

### **Device Generic Name**

Cardiac Support Device (CSD)

Accessories:

Cardiac Support Device Cord Sizer (Cord Sizer)

Cardiac Support Device Tape Sizer (Tape Sizer)

Cardiac Support Device Cord Sizer Handles (Cord Sizer Handles)

Cardiac Support Device Fitting Clamp

### **Device Trade Name**

CorCap™ Cardiac Support Device (CSD)

Accessories:

CorCap cord sizer (Cord Sizer)

CorCap tape sizer (Tape Sizer)

CorCap cord sizer handles (Cord Sizer Handles)

CorCap 12 cm fitting clamp

CorCap 15 cm fitting clamp

### **Applicant Name and Address**

Acorn Cardiovascular, Inc.

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## **Manufacturer Name and Address**

Acorn Cardiovascular, Inc.  
601 Campus Drive  
St. Paul, MN 55112  
Manufacturer of CorCap CSD, CorCap Cord Sizer, & CorCap Tape Sizer

## **Contract Manufacturer Name and Address**

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St. Paul, Minnesota 55107  
FDA Establishment Registration Number: 2126670  
Manufacturer of CorCap Fitting Clamp

## **B. Indications for Use/Intended Use**

### **Indications**

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 (LVEDD  $\geq$  60mm or LVEDDI  $\geq$  30mm/m<sup>2</sup>) and an LVEF  $\leq$  35% (LVEF  $\leq$  45% if planned mitral valve repair or replacement).

### **Intended Use**

The CorCap CSD provides beneficial changes in cardiac structure associated with a reverse remodeling effect as defined by a reduction in left ventricular (LV) size, an increase in LVEF, and a change to a more elliptical shape. The CorCap CSD also provides a decrease in the need for additional major cardiac procedures associated with the progression of heart failure and an overall improvement in quality of life.

## **C. CorCap CSD Device Description**

The CorCap CSD is constructed from polyester fabric and PTFE-coated polyester non-absorbable suture material. The CorCap CSD is offered in multiple sizes to accommodate different heart sizes.

## **D. Contraindications, Warnings, and Precautions**

### **1. CONTRAINDICATIONS**

Patients with any condition considered to be a contraindication for cardiac surgery should not undergo surgery for implant of the CorCap CSD.

### **2. WARNINGS**

- Do not perform procedure in patients with an active infection.
- Do not perform procedure in patients with primary restrictive disease.
- Patients who are not good candidates for cardiac surgery (i.e., patients diagnosed with end-stage NYHA functional class IV or patients dependent upon intravenous inotropes, intra aortic balloon pump, and/or left ventricular assist device) may not be suitable candidates for CorCap CSD therapy.
- Placement of device over pre-existing coronary artery bypass grafts has not been evaluated and may compromise graft patency.
- In patients with previous CorCap CSD implant, location of appropriate anastomotic sites for coronary artery bypass surgery may be extremely difficult.
- Patients undergoing cardiac surgery may be at a greater risk for development of fibrosis and adhesions. This could potentially increase the surgical time required for subsequent cardiac surgeries.

### **3. PRECAUTIONS**

- Patients with hypertrophic obstructive cardiomyopathy or primary diastolic dysfunction may not benefit from the CorCap CSD implant.
- Procedure may not be possible in patients with profound cardiomegaly (>14.6 cm external cardiac diameter), which exceeds the largest CorCap CSD size available.
- As with any cardiac surgery, use of an adhesion barrier may be considered, particularly in patients with an increased potential for requiring future operations.
- Procedure requires ability to obtain complete circumferential access to the heart, which may be compromised in patients with pre-existing pericardial or epicardial adhesions.
- Alteration to the device or implant procedure beyond these instructions may result in unknown device performance.
- Direct application of antibiotics to the CorCap CSD should be avoided.
- Patient risks or discomforts expected include standard risks of a patient undergoing cardiothoracic surgery. These may include: bleeding; development of cardiac pulmonary embolism, infarct, or peripheral embolism; hemodynamic compromise potentially leading to cardiogenic

shock and/or neurological deficit; infection; pneumonia; pulmonary, renal, or hepatic compromise potentially leading to failure; death; other surgical trauma; reoperation; and/or allergic response to anesthesia, medications or device material.

- Use of an IABP is recommended in patients where manipulation of the heart could cause hemodynamic instability.
- If hemodynamic instability cannot be managed by pharmacological means, CPB is recommended.

## **E. Alternative Practices and Procedures**

Available therapies for the treatment of heart failure and its associated symptoms include pharmacologic therapy, cardiac rhythm management, and surgical interventions (such as mitral valve repair, coronary artery bypass grafting and aneurysmectomy, for patients having these surgical needs). Patients in end-stage heart failure may be candidates for LVAD implantation or heart transplantation.

## **F. Marketing History**

The CorCap CSD received CE Marking for concomitant use in September of 2000 and CorCap CSD only use in April 2001. As of December 1, 2004, a total of 174 CorCap CSDs were implanted in patients from five European countries including France, Germany, Netherlands, Sweden, and Italy. The CorCap CSD has not had any issues in the countries listed for reasons related to the safety and effectiveness of the device.

## **G. Summary of Pre-Clinical Studies**

### **ANIMAL STUDIES**

Numerous animal studies were conducted with the CorCap CSD to determine device design feasibility, evaluate device safety and efficacy, and determine optimal materials, performance characteristics and implant methods. These studies established baseline specifications and demonstrated initial safety and efficacy of the CorCap CSD. **Table 1** provides a summary of the animal studies conducted.

**Table 1: Summary of Animal Studies**

|   | <b>Study Title</b>  | <b>Purpose</b>   | <b>Results/Conclusions</b>  |
|---|---|--|---|
| 1 | Efficacy to Inhibit Progressive Left Ventricular Dilatation in Canine Model | <ul style="list-style-type: none"> <li>• Determine S&amp;E in ischemic cardiomyopathy</li> <li>• Characterize cellular and histomorphometric response</li> <li>• Evaluate histological reaction and healing response</li> </ul>    | <ul style="list-style-type: none"> <li>• No complications</li> <li>• CorCap CSD maintained or decreased ventricular volumes, stroke volumes</li> <li>• CorCap CSD increased ejection fraction</li> <li>• CorCap CSD eliminated mitral valve regurgitation</li> <li>• CorCap CSD subjects showed improvement in size of myocytes, oxygen diffusion distance and capillary density</li> </ul> |
| 2 | Proof of Concept: Rapid Pacing Sheep Model                                  | <ul style="list-style-type: none"> <li>• Establish performance criteria</li> <li>• Establish implant technique</li> <li>• Establish cardiac performance effect</li> </ul>  | <ul style="list-style-type: none"> <li>• No morbidity or mortality</li> <li>• Mitral valve competence maintained</li> <li>• Prevention of continuing remodeling</li> </ul>  |
| 3 | Historical Device Design & Safety: Normal Canine Model                      | <b>Phase I</b>   |   |
|   |   | <ul style="list-style-type: none"> <li>• Determine optimal material</li> <li>• Determine optimal weave design</li> <li>• Evaluate safety</li> </ul>  | <ul style="list-style-type: none"> <li>• Optimal material and weave selected</li> <li>• No complications or adverse events observed</li> </ul>  |
|   |   | <b>Phase II</b>  |   |
|   |   | <ul style="list-style-type: none"> <li>• Measure cardiac functional changes</li> <li>• Determine pathologic and histologic responses</li> <li>• Evaluate safety</li> </ul>   | <ul style="list-style-type: none"> <li>• No changes in ventricular function (ejection fraction, LVEDV, LVEDV, stroke volume)</li> <li>• No changes in ventricular filling pressures or ventricular relaxation times</li> </ul>  |
|   | Analysis of Volume Loading: Acute and Chronic Canine Model                  | <ul style="list-style-type: none"> <li>• Determine cardiac functional responses during pre-load challenge</li> <li>• Identify potential adverse effects during pre-load challenge</li> </ul>                                       | <ul style="list-style-type: none"> <li>• Response to stress was an increase in stroke volume without development of cardiac constriction</li> <li>• No significant change in any of the measured ventricular pressure parameters (mean LVEDP, LVESP and mean RVEDP) were reported</li> <li>• No adverse reactions or animal deaths occurred</li> </ul>                                      |
| 4 | Evaluation in a Normal Canine   | <ul style="list-style-type: none"> <li>• Evaluate cardiac function with long-term chronic CorCap CSD implant</li> <li>• Histologic evaluation of reaction to CorCap CSD</li> <li>• Evaluate CorCap CSD device integrity</li> </ul> | <ul style="list-style-type: none"> <li>• No significant changes in LV function or RV pressures compared to baseline</li> <li>• One animal death at 9-days post implant (implant group); investigator did not believe death was device-related</li> <li>• No infection or inflammatory reaction</li> </ul>   |

**Table 1 (continued): Summary of Animal Studies**

|   | Study Title   | Purpose  | Results/Conclusions  |
|---|---|--|--|
| 5 | Acute Ventricular Reshaping in Advanced Canine Heart Failure  | <ul style="list-style-type: none"> <li>• Determine if CorCap CSD can maintain an acutely reduced left ventricle</li> <li>• Determine if acute left ventricular reduction is associated with maintenance of left ventricular function in this failure model</li> <li>• Assess the potential for acute or chronic adverse effects of acute ventricular reduction</li> </ul>  | <ul style="list-style-type: none"> <li>• No constrictive pattern observed</li> <li>• Significantly reduced left ventricular end diastolic &amp; end systolic volumes &amp; dimensions</li> <li>• Significantly increased left ventricular ejection fraction</li> <li>• Eliminated mitral valve regurgitation (5 of 7 animals)</li> <li>• One treatment animal died 1-week post-implant; death attributed to follow-up catheterization procedure</li> <li>• No other acute or chronic safety issues observed</li> <li>• Improved cardiac reserve</li> </ul>         |
| 6 | Safety and Efficacy in Ovine Advanced Dilated Cardiomyopathy  | <ul style="list-style-type: none"> <li>• Determine impact of CorCap CSD on cardiac function in hearts with moderate and severe dilated cardiomyopathy compared to Control</li> <li>• Determine cardiac functional changes using an exercise test</li> <li>• Determine the pathologic and histologic response CorCap CSD at 6 &amp; 12 months</li> <li>• Determine safety and efficacy of CorCap CSD in dilated cardiomyopathy</li> </ul> | <ul style="list-style-type: none"> <li>• No negative chronic reaction to CorCap CSD material</li> <li>• No observed morbidity or mortality associated with chronic device implant</li> <li>• No adverse impact on epicardial vasculature</li> <li>• All animals survived the planned high-rate paced study period, the initial implant period, and chronic phase</li> <li>• No implanted animals demonstrated complications due to the device</li> <li>• There was no evidence of myocardial infarction or constriction in any of the implanted animals</li> </ul> |
| 7 | Comparative Study of Material Properties in Normal Canine   | <ul style="list-style-type: none"> <li>• Evaluate 30 day biological reaction to CorCap CSD manufactured from fabric with an increased hole count and thickness</li> <li>• Evaluate epicardial fibrosis measurements for CorCap CSD and Control groups</li> </ul>   | <ul style="list-style-type: none"> <li>• No significant differences in hemodynamic performance</li> <li>• No deaths or complications related to device implant</li> <li>• All implanted animals survived the 30 day implant period without surgery-related complications</li> </ul>  |
| 8 | Long-Term Hemodynamic and Histologic Response: Canine Ischemic Injury Model                               | <ul style="list-style-type: none"> <li>• Evaluate safety and long-term histological response to implant of the CorCap CSD in a canine heart failure model</li> </ul>   | <ul style="list-style-type: none"> <li>• No morbidity or mortality associated with the device</li> <li>• Cardiac structure and function showed improvement 6 months post-implant</li> </ul>  |
| 9 | Effects of Ventricular Constraint in Advanced Heart Failure: Canine Microembolization Heart Failure Model | <ul style="list-style-type: none"> <li>• Examine long-term effects on cardiac structure and function</li> <li>• Examine long-term effects on tissue structure</li> </ul>   | <ul style="list-style-type: none"> <li>• Decrease in heart size for CorCap CSD group (LVEVD, LVESD);</li> <li>• Decrease in individual cardiomyocyte size in CorCap CSD group compared to control</li> </ul>   |

## MATERIAL CHARACTERIZATION AND BIOCOMPATIBILITY STUDIES

Material and device characterization testing was conducted to demonstrate that manufacturing processes do not introduce any toxic residuals or cause any damage to the material that may result in adverse biological response. Biocompatibility testing was conducted to evaluate potential mechanisms of toxicity per ISO 10993. Results demonstrated that the manufacturing process does not introduce toxins or damage devices and that the CorCap CSD does not generate an adverse biological response. **Table 2** and **Table 3** provide summaries of the studies conducted.

**Table 2: Summary of Material and Device Characterization Studies**

|    | Test  | Purpose  | Results |
|----|---|--|---------|
| 1. | CorCap CSD Polyester Yarn Characterization: Polymer Analysis    | <ul style="list-style-type: none"> <li>• Molecular weight distribution through gel permeation chromatography</li> <li>• Intrinsic viscosity through dilute solution</li> <li>• Identification through Fourier transform infrared spectroscopy</li> <li>• Melting point through differential scanning calorimetry</li> <li>• Crystallinity through differential scanning calorimetry</li> <li>• Pigment content/ash analysis through pyrolysis</li> <li>• Extractables through solvent extraction</li> <li>• Carboxyl end groups through acid value</li> <li>• Diethylene glycol content through gas chromatography</li> <li>• Catalyst and trace elements through inductively coupled plasma optical emission</li> </ul> | Pass    |
| 2. | CorCap CSD Polyester Yarn Characterization: Spin Finish         | <ul style="list-style-type: none"> <li>• Percent add-on through solvent extraction</li> <li>• Identification of components through Fourier transform infrared spectroscopy and high-performance liquid chromatography</li> </ul>   | Pass    |
| 3. | CorCap CSD Polyester Yarn Characterization: Physical Properties | <ul style="list-style-type: none"> <li>• Linear density</li> <li>• Filament count</li> <li>• Tensile Properties</li> <li>• Bulk shrinkage</li> <li>• Coefficient of friction</li> <li>• Cross-section and surface analysis through photomicroscopy</li> </ul>  | Pass    |
| 4. | CorCap CSD Device Characterization: Polymer Analysis            | <ul style="list-style-type: none"> <li>• Fourier transform infrared spectroscopy</li> <li>• Differential scanning calorimetry</li> <li>• Dynamic mechanical analysis</li> </ul>  | Pass    |
| 5. | CorCap CSD Device Characterization: Extractables                | <ul style="list-style-type: none"> <li>• Sequential solvent extraction method</li> </ul>   | Pass    |
| 6. | CorCap CSD Device Characterization: EtO Residuals               | <ul style="list-style-type: none"> <li>• Measure EtO residuals per ISO 10993; maximum daily dose limited to 12 mg of ethylene chlorohydrin for a permanent implant device</li> </ul>   | Pass    |
| 7. | CorCap CSD Device Characterization: LAL                         | <ul style="list-style-type: none"> <li>• Examine LAL to determine the level of endotoxins per USP 23; maximum acceptable limit of 20 EU/device</li> </ul>  | Pass    |
| 8. | CorCap CSD Device Characterization: Bioburden Testing           | <ul style="list-style-type: none"> <li>• Examined device bioburden to determine number of viable organisms on devices prior to sterilization; no limit criteria for this testing, but it is useful to monitor bioburden as indicator of production process quality</li> </ul>  | Pass    |

**Table 3: Summary of Biocompatibility Studies**

|    | Test                               | Purpose   | Results   |
|----|------------------------------------|---|---|
| 1. | Cytotoxicity                       | Determine level of reactivity                     | No cellular reactivity  |
| 2. | Sensitization                      | Determine level of reactivity                     | No dermal reactivity  |
| 3. | Irritation/Intracutaneous Toxicity | Determine level of reactivity                     | No dermal reactivity or toxicity                              |
| 4. | Systemic Toxicity                  | Determine whether CorCap CSD is an irritant       | No signs of systemic toxicity                                 |
| 5. | Genotoxicity/Gene Mutation         | Determine level of genotoxic reactivity           | No statistical data showing a change in reverse mutation rate |
| 6. | Implantation (short-term)          | Determine level of cellular and fibrotic response | Reaction consistent with PET                                  |
| 7. | Implantation (long-term)           | Determine level of cellular and fibrotic response | Reaction consistent with PET                                  |
| 8. | Pyrogenicity                       | Determine absence/presence of pyrogens            | Non-pyrogenic   |

## ENGINEERING STUDIES

Engineering/Bench testing was conducted to simulate *in vivo* design requirements for the CorCap CSD. The physical performance parameters evaluated included testing of the following dimensional and mechanical aspects of the device:

- Dimensional Evaluations (hole opening density; fabric, seam, and hem thickness)
- Tensile Strength (fabric, seam)
- Suture Tear-out (fabric, tissue)
- Run and Unravel Resistance
- Fabric Compliance
- Sewn Feature Compliance (seam, hem)
- Durability Testing

**Table 4** provides a summary of the engineering studies conducted.

**Table 4: Summary of Engineering/Bench Testing Studies**

|   | Study Title  | Purpose   | Results/Conclusions   |
|---|--|---|---|
| 1 | CorCap CSD Design Qualification  | Qualify the CorCap CSD design and manufacturing process against the product specification   | CorCap CSD meets specifications   |
| 2 | CorCap CSD Suture Tear-Out   | Examine the ability of cardiac tissue to resist the tearing-out of stay suture  | Results of testing met specification; testing indicates that sutures perpendicular to AV groove may be stronger than parallel   |
| 3 | CorCap CSD Design Qualification: New Packaging Configuration and 15 month Shelf Life | Verify that the thermoformed tray packaged CorCap CSD meets the design requirements after sterilization, accelerated aging and distribution simulation (15 months of accelerated aging)     | CorCap CSD meets specifications   |
| 4 | CorCap CSD Design Qualification: New Packaging Configuration and 37 month Shelf Life | Verify that the thermoformed tray packaged CorCap CSD meets the design requirements after sterilization, and accelerated aging and distribution simulation (37 months of accelerated aging) | CorCap CSD meets specifications   |
| 5 | CorCap CSD Durability Testing  | Demonstrate that the CorCap CSD is durable and can sustain the maximum intended design load beyond the number of cycles that would occur during 5 years of implant                          | The CorCap CSD supported the design load during one billion cycles of accelerated <i>in vitro</i> testing designed to simulated implanted loading conditions with no mechanical deterioration or failure; this is equivalent to approximately 25 years of implant duration at a heart rate of 76 beats per minute |

## STERILIZATION, PACKAGING, AND SHELF-LIFE STUDIES

Sterilization validation studies were conducted to ensure that the CorCap CSD sterilization process provides a minimum sterility assurance level (SAL) of  $10^{-6}$  per ISO 11135. Accelerated-aged CorCap CSDs were subjected to distribution/shipping simulation, peel seal and dye penetration testing, and functional testing (in that order) to demonstrate that aging and shipping do not compromise the packaging, sterile barrier integrity, or device integrity/functionality. **Table 5** provides a summary of the studies conducted.

**Table 5: Summary of Sterilization, Packaging, and Shelf-Life Studies**

|    | Title                                     | Purpose  | Results  |
|----|---|--|--|
| 1. | CorCap CSD Sterilization Validation       | Demonstrate that EtO Sterilization Cycle Meets criteria detailed in ISO 11135  | Pass; EtO cycle delivers minimum SAL of $10^{-6}$      |
| 2. | CorCap CSD 37-Month Shelf Life Validation | Demonstrate that CorCap CSD product and packaging meet established specifications after accelerated aging and simulated shipping; establish product shelf life | Pass;<br>Product labeled with 37 month Expiration Date |

## **H. Adverse Events**

### **1. POTENTIAL ADVERSE EVENTS**

Based on the literature review of cardiac surgery experience and clinical trial experience with the CorCap CSD, the following alphabetical list includes possible adverse events associated with implantation of the CorCap CSD:

- Allergic response
- Bleeding (internal and external)
- Cardiac arrhythmias
- Cardiac tamponade
- Chronic pain
- Death
- Fibrotic tissue formation (e.g., keloid formation)
- Hemodynamic compromise potentially leading to cardiogenic shock and/or neurological deficit
- Infection, sepsis
- Local tissue reaction
- Myocardial infarction
- Other surgical trauma
- Pericardial effusion
- Pericarditis
- Pneumothorax
- Pulmonary, renal, or hepatic compromise potentially leading to failure
- Reoperation
- Thromboembolism

## 2. OBSERVED ADVERSE EVENTS

**Table 6** provides the number of patients experiencing an adverse event by treatment group throughout the entire duration of study follow-up (*updated on 15 April 2005*). There were no device-related adverse events in this study. The left hand columns report any adverse events while the right hand columns report only the adverse events that met the definition of “serious.” The total number of patients that experienced a serious adverse event was not statistically different between the treatment and control groups. There was a significant difference in patients experiencing a hemodynamic compromise serious adverse event between treatment and control ( $p=0.04$  favoring treatment). There were no adverse events reported related to sizing or fitting of the CorCap CSD.

**Table 6: Patients Experiencing Adverse Events**  
(p-values obtained from CMH)

|                                 | Any Adverse Event    |             |                    |             |             | Any Serious Adverse Event |             |                    |             |             |
|---------------------------------|----------------------|-------------|--------------------|-------------|-------------|---------------------------|-------------|--------------------|-------------|-------------|
|                                 | Treatment<br>(n=148) |             | Control<br>(n=152) |             | p-<br>value | Treatment<br>(n=148)      |             | Control<br>(n=152) |             | p-<br>value |
|                                 | #<br>Pts             | % of<br>148 | #<br>Pts           | % of<br>152 |             | #<br>Pts                  | % of<br>148 | #<br>Pts           | % of<br>152 |             |
| Allergic Response               | 3                    | 2.0         | 1                  | 0.7         | 0.22        | 3                         | 2.0         | 1                  | 0.7         | 0.22        |
| Arrhythmia                      | 62                   | 41.9        | 66                 | 43.4        | 0.99        | 51                        | 34.5        | 60                 | 39.5        | 0.46        |
| Bleeding                        | 10                   | 6.8         | 16                 | 10.5        | 0.26        | 9                         | 6.1         | 15                 | 9.9         | 0.23        |
| Hemodynamic<br>Compromise       | 90                   | 60.8        | 75                 | 49.3        | 0.05        | 90                        | 60.8        | 74                 | 48.7        | 0.04        |
| Hepatic Compromise              | 2                    | 1.4         | 0                  | 0.0         | 0.14        | 2                         | 1.4         | 0                  | 0.0         | 0.14        |
| Infection/Pneumonia             | 55                   | 37.2        | 46                 | 30.3        | 0.16        | 47                        | 31.8        | 37                 | 24.3        | 0.11        |
| Myocardial Infarction           | 1                    | 0.7         | 2                  | 1.3         | 0.56        | 1                         | 0.7         | 2                  | 1.3         | 0.56        |
| Neurological<br>Deficit/Stroke  | 19                   | 12.8        | 12                 | 7.9         | 0.13        | 16                        | 10.8        | 12                 | 7.9         | 0.34        |
| Peripheral<br>Thrombus/Embolism | 6                    | 4.1         | 3                  | 2.0         | 0.26        | 4                         | 2.7         | 3                  | 2.0         | 0.63        |
| Pulmonary<br>Compromise         | 31                   | 20.9        | 23                 | 15.1        | 0.14        | 31                        | 20.9        | 23                 | 15.1        | 0.14        |
| Pulmonary Embolism              | 3                    | 2.0         | 2                  | 1.3         | 0.62        | 3                         | 2.0         | 2                  | 1.3         | 0.62        |
| Renal Compromise                | 17                   | 11.5        | 8                  | 5.3         | 0.05        | 17                        | 11.5        | 8                  | 5.3         | 0.052       |
| Other                           | 63                   | 42.6        | 63                 | 41.4        | 0.81        | 63                        | 42.6        | 61                 | 40.1        | 0.62        |
| Any of the Above AE             | 129                  | 87.2        | 124                | 81.6        | 0.15        | 123                       | 83.1        | 120                | 78.9        | 0.33        |

Kaplan Meier analysis of freedom from SAEs or death is summarized in **Figure 1**.

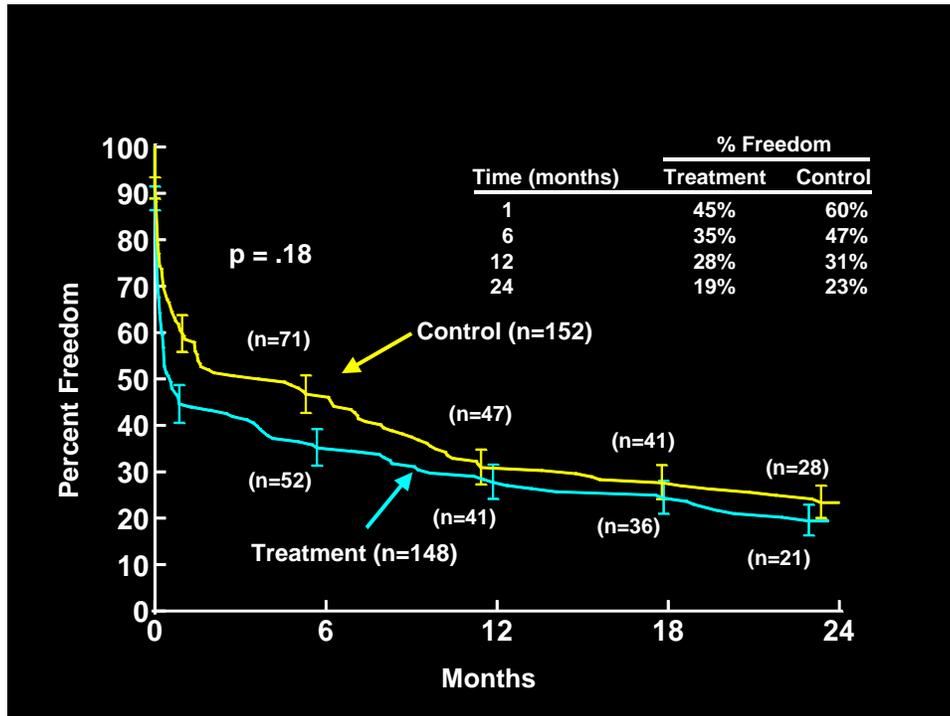


Figure 1: Freedom From SAE or Death (Updated 15 April 2005)

Both groups demonstrate high incidence of SAEs in the first 30 days, without any significant difference between treatment and control groups.

## I. Summary of Clinical Studies

The study Clinical Evaluation of the Acorn Cardiac Support Device Therapy in Patients with Dilated Cardiomyopathy – A Randomized Trial in the United States and Canada was initiated by Acorn Cardiovascular Inc., under the approved IDE G990267 in June 2000.

### 1. STUDY DESIGN OVERVIEW

This study was a 300 patient prospective, randomized, controlled, multi-center trial. Patients were randomly allocated to receive the CorCap CSD implant with or without mitral valve repair or replacement (MVR) or to the control group with or without MVR. All patients in the treatment and control groups received optimal medical therapy.

## 2. STUDY HYPOTHESIS

CorCap CSD therapy will improve patient functional status (improved, same, worsened) as measured by a clinical composite consisting of mortality, major cardiac procedures, and change in NYHA class.

## 3. OBJECTIVES

### Primary Objective

To compare patient functional status after a minimum of 12 months of follow-up for patients randomly assigned to treatment (CorCap CSD implant) or control (no CorCap CSD implant).

### Secondary Objectives

To determine the rate of death and other serious adverse events experienced by patients assigned to the CorCap CSD implant and to compare this rate with that for patients assigned to the control group.

To compare patient functional status and structural changes in the heart for the treatment and the control groups.

## 4. PRIMARY COMPOSITE ENDPOINT

The primary endpoint was a composite ordinal endpoint based on 1) death, 2) major cardiac procedures indicative of progression of heart failure, and 3) change in core lab assessment of New York Heart Association (NYHA) functional classification.

At the end of the study, patients assigned to the treatment group were compared to patients assigned to the control group for assessment of their functional status as follows:

**Worsened**-patient died, experienced a major cardiac procedure or was classified as at least one category worse on core lab NYHA as compared to baseline.

**Same**-patient is alive, did not experience a major cardiac procedure and was classified as the same on core lab NYHA as compared to baseline.

**Improved**-patient is alive, did not experience a major cardiac procedure and was classified as at least one category improved on core lab NYHA as compared to baseline.

## 5. SECONDARY EFFICACY ENDPOINTS

The following secondary endpoints were assessed compared to baseline measurement (pre-randomization):

- Change in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV)
- Change in left ventricular ejection fraction (LVEF) as measured via echocardiography.
- Change in quality of life as determined from the Minnesota Living with Heart Failure (MLHF) and SF-36 questionnaires.
- Change in NYHA functional class as determined by the site clinician and the core lab clinician.
- Change in left ventricular end-diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), mitral regurgitation and sphericity as measured via echocardiography.
- Number of hospitalizations, hospital days and ICU days, cardiac related and overall.
- Change in exercise status as measured by 6-minute walk distance.
- Change in peak oxygen consumption and anaerobic threshold as measured on the cardiopulmonary exercise test (CPX).
- Change in B-type natriuretic peptide (BNP) content in blood plasma.
- All-cause mortality and re-hospitalization.
- Incidence of major cardiac procedures.

## 6. INCLUSION CRITERIA

- Dilated cardiomyopathy of either ischemic or non-ischemic origin.
- Stable and optimal medical management including all of the following:
  - Angiotensin-converting enzyme inhibitors (ACE) or alternate if ACE not tolerated
  - Diuretic at least “prn” (as occasion required)
  - Treatment with a beta-blocker (unless intolerant) for  $\geq 3$  months (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention)
  - Cardiac medications unchanged for  $\geq 1$  month except for diuretic adjustments (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention)
- Adult (18-80 years).
- Left ventricular end-diastolic dimension (LVEDD)  $\geq 60$  mm or LVEDD index  $\geq 30$  mm/m<sup>2</sup> as determined by transthoracic echocardiography.
- Mitral regurgitation (MR)  $\leq 2+$  unless scheduled for MVR.

- Signed Informed Consent.
- Left ventricular ejection fraction (LVEF)  $\leq$  35% via transthoracic echocardiography, cardiac catheterization, radionuclide scan or magnetic resonance imaging or LVEF  $\leq$  45% and planned MVR.
- New York Heart Association Functional Class (NYHA) III or IV or NYHA II if scheduled MVR.
- Baseline 6-minute walk distance  $<$  450 meters (1476 feet).
- Acceptable hepatic function with serum glutamic oxalo-acetic transaminase (SGOT or AST) and serum glutamic pyruvic transaminase (SGPT or ALT)  $<$  3X upper limit of normal.
- Acceptable pulmonary function as assessed clinically unless there is history of compromise or current evidence of compromise, in which case forced expiratory volume in the first second (FEV1) must be  $>$  50% of predicted normal value.
- Geographically available for follow-up.

## 7. EXCLUSION CRITERIA

- Planned cardiac surgical procedure other than MVR with or without tricuspid valve repair or atrial fibrillation ablation procedure.
- Hypertrophic obstructive cardiomyopathy.
- Significant cardiomegaly, which is estimated to exceed the largest available size of Cardiac Support Device.
- Expectation of existing cardiothoracic adhesions that would cause an inability to gain complete circumferential access to the heart.
- Any condition considered a contraindication for extracorporeal circulation.
- Late-stage heart failure with increased surgical risk as defined by the presence of **four** or more of the following:
  - LVEDD  $\geq$  80 mm
  - Peak  $VO_2 \leq$  13 ml/kg/min (cardiopulmonary exercise test)
  - Resting systolic BP  $\leq$  80 mmHg (on clinical exam)
  - Atrial fibrillation at time of enrollment or paced rhythm with underlying atrial fibrillation
  - Heart failure duration  $\geq$  8 years
  - Exercise-induced increase in systolic BP  $\leq$  10% (cardiopulmonary exercise test)
  - 6-minute walk  $\leq$  350 meters (1148 feet)
  - Previous cardiac surgery
  - BUN  $\geq$  100 mg/dl
  - Cachexia (clinical impression)
- Existing patent CABG.
- Candidates for surgical revascularization as determined by an angiogram. Patients with ischemic heart disease who have not had an

angiogram within the past 3 years and in whom lesions amenable to revascularization cannot be excluded should have a repeat angiogram.

- Receiving an IABP, intravenous inotropic or vasoactive agents, except for immediate pre-operative hemodynamic optimization.
- Current or anticipated need for left ventricular assist device (LVAD) or cardiac replacement device.
- On active transplant list or anticipated need for heart transplant within the next two years.
- Acute myocardial infarction, unstable angina or cerebral vascular accident (TIA or CVA) within the past 3 months.
- Percutaneous coronary intervention or transmyocardial laser revascularization (TMR or PMR) within the past 3 months.
- Presence of arrhythmias causing hemodynamic instability, history of resuscitated sudden death without subsequent treatment with implantable defibrillator or amiodarone or atrial fibrillation with a ventricular rate > 100 bpm on medication.
- Co-morbid condition that reduces life expectancy to less than 1 year.
- Serum creatinine  $\geq$  3.5 mg/dl or dialysis dependent.
- Bi-ventricular (BiV) pacing initiated within the past 3 months or anticipated within the next 12 months.
- Active infection.
- Pregnancy at the time of enrollment. (Women of child bearing potential must have a negative serum pregnancy test within two weeks prior to randomization, or must be using hormonal contraceptives or intrauterine devices.)
- Enrolled in another investigational study that would confound interpretation of trial results, or receiving experimental or investigational drugs.
- Unable to comply with protocol-required follow-up (as judged by primary investigator or referring cardiologist).

## **8. IRB APPROVAL, PATIENT SCREENING, INFORMED CONSENT**

Prior to initiating enrollment, each site submitted appropriate study information and consent forms to their Institutional Review Board (IRB) or Ethics Committee for review and approval. After receiving approval for the protocol and consent forms, sites were allowed to approach patients and invite participation. Prior to undergoing study-required testing and enrollment, the study was explained to the patient by the investigator or a trained clinical professional. If the patient decided to participate, a consent form was provided in the patient's native language.

## 9. CORE LABS

There were four core labs used for this study to reduce potential bias (independent, blinded) and variation between center analyses:

- Echocardiogram
- B-type natriuretic peptide (BNP)
- Cardiopulmonary Exercise
- New York Heart Association (NYHA) Classification

## 10. PATIENT ASSESSMENT

Pre-enrollment and follow-up testing is summarized in **Table 8**.

**Table 8: Pre-enrollment and Follow-up Testing**

| Test  | Pre-enrollment              | 3 Months ( $\pm$ 1 month) | 6 Months ( $\pm$ 1 month) | 12 Months & every 6 Months thereafter ( $\pm$ 3 months) until 4 Jul04 |
|---|-----------------------------|---------------------------|---------------------------|---|
| Clinical Assessment   | X                           | X                         | X                         | X   |
| Core Lab NYHA Assessment  | X                           |                           | X                         | X   |
| Chest X-ray   | X<br>(within past 3 months) |                           |                           |   |
| Blood Tests   | X                           | X                         | X                         | X   |
| BNP   | X                           | X                         | X                         | X   |
| Echocardiography (transthoracic)  | X                           | X                         | X                         | X   |
| ECG   | X<br>(within past 3 months) | X                         | X                         | X (Stop after 12 months)  |
| Cardiopulmonary Exercise Test   | X<br>(within past 3 months) |                           | X                         | X (Stop after 12 months)  |
| Six Minute Walk   | X                           | X                         | X                         | X   |
| MLHF and SF-36 Questionnaires   | X                           | X                         | X                         | X   |
| Right and/or Left Heart Catheterization   | X*                          |                           |                           |   |
| <ul style="list-style-type: none"> <li>◆ Information regarding vital status and adverse events were reported as they occurred.</li> <li>◆ 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.</li> <li>◆ Follow-up testing was supplemented by regularly scheduled telephone assessment performed according to the following schedule:               <ul style="list-style-type: none"> <li>◆ Every 2 weeks through week 10</li> <li>◆ Monthly between months 4 and 12</li> <li>◆ Quarterly after month 12 (every 3 months)</li> </ul>               Telephone assessment was not required during intervals when the patient was seen for a follow-up visit.             </li> </ul> <p>*As required for patients with ischemic heart disease.</p> |                             |                           |                           |   |

## 11. INVESTIGATIONAL SITES

Each site had two principal investigators; one surgeon and one cardiologist. Twenty-nine sites enrolled a total of 300 patients.

## 12. BASELINE CHARACTERISTICS

**Table 9** summarizes the gender, age, race, and heart failure etiology at baseline. In general, patients in this trial were similar to many other heart failure trials with a few notable exceptions. Patients enrolled in this study were younger (mean age 52.5 years) than patients typically enrolled in heart failure population trials,<sup>1,2,3,4</sup> in which the mean age is generally 60-70 years. There were 45% females enrolled in this study which is a higher percentage than most other heart failure trials.<sup>5,6,7,8,9</sup> Thirty-five percent of patients were non-Caucasian. The most common etiology of heart failure was idiopathic (61%). In contrast, the most frequent etiology of heart failure in other trials is ischemic heart disease. The low percentage of ischemic patients was likely due to the fact that concomitant coronary arterial bypass graft (CABG) surgery was not permitted. Etiologies classified as “other” included adriamycin, post partum, familial, chemotherapy, radiation, dietary, HIV related, myocarditis, chemical exposure, peripartum, and hyperthyroid induced heart disease.

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<sup>1</sup> Abraham WB et. al., “Cardiac Resynchronization in Chronic Heart Failure,” *The New England Journal of Medicine*, Vol. 346, No. 24, pp. 1845-1853, June 13, 2002.

<sup>2</sup> Bristow MB, et. al., “Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure,” *The New England Journal of Medicine*, Vol. 350, No. 21, pp. 2140-2150, May 20, 2004.

<sup>3</sup> St. Jude Medical Cardiac Rhythm Management Division, “Summary of Safety and Effectiveness Data for Dual Chamber Implantable Cardioverter Defibrillator (ICD) with Cardiac Resynchronization Therapy,” Premarket Approval Application Number P030054, 2004.

<sup>4</sup> Thoratec Corporation, “Summary of Safety and Effectiveness Data for Ventricular Assist Device,” Premarket Approval Application Number P920014/S016, 2002.

<sup>5</sup> Ibid.

<sup>6</sup> St. Jude Medical, ID.

<sup>7</sup> Kadish A, et. al., “Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy,” *The New England Journal of Medicine*, Vol. 350, No. 21, pp. 2151-2158, May 20, 2004.

<sup>8</sup> Bristow MB, et. al., Id.

<sup>9</sup> Abraham WB et. al., Id.

**Table 9: Age, Gender, Race and Etiology at Baseline**

|                                     | # Pts | Mean or %  |
|-------------------------------------|-------|------------|
| Age (mean years)                    | 300   | 52.5 years |
| Gender                              |       |            |
| Male                                | 166   | 55.3%      |
| Female                              | 134   | 44.7%      |
| Race                                |       |            |
| White                               | 195   | 65.0%      |
| Black                               | 81    | 27.0%      |
| Other                               | 24    | 8.0%       |
| Etiology                            |       |            |
| Ischemic                            | 30    | 10.0%      |
| Idiopathic                          | 184   | 61.3%      |
| Viral                               | 25    | 8.3%       |
| Alcoholic                           | 6     | 2.0%       |
| Valvular                            | 34    | 11.3%      |
| Hypertensive                        | 30    | 10.0%      |
| Other                               | 25    | 8.3%       |
| Years Since Heart Failure Diagnosis | 300   | 5.0 years  |

**Table 10** summarizes the cardiac medications at baseline for all patients. A total of 97% of all patients were on an ACE Inhibitor or Angiotensin II Blocker and 85% of all patients were on a beta-blocker at the time of enrollment.

The percentage of patients on an ACE inhibitor/Angiotensin II blocker and beta-blocker were among the highest percentages of all previous trials in heart failure.<sup>10,11,12,13,14</sup> This provides strong evidence that enrolled patients were on a maximal and optimal medication regimen prior to entry into this study and reflects the comprehensive medical care provided by the sites. The fact that greater than

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<sup>10</sup> Abraham WB et. al., “Cardiac Resynchronization in Chronic Heart Failure,” The New England Journal of Medicine, Vol. 346, No. 24, pp. 1845-1853, June 13, 2002.

<sup>11</sup> Bristow MB, et. al., “Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure,” The New England Journal of Medicine, Vol. 350, No. 21, pp. 2140-2150, May 20, 2004.

<sup>12</sup> St. Jude Medical Cardiac Rhythm Management Division, “Summary of Safety and Effectiveness Data for Dual Chamber Implantable Cardioverter Defibrillator (ICD) with Cardiac Resynchronization Therapy,” Premarket Approval Application Number P030054, 2004.

<sup>13</sup> Medtronic, Inc., “Summary of Safety and Effectiveness Data for InSync® ICD Model 7272 Dual Chamber Implantable Cardioverter Defibrillator with Cardiac Resynchronization Therapy and the Model 9969 Application Software,” Premarket Approval Application Number P010031, 2002.

<sup>14</sup> Higgins SL, et. al., “Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias,” Journal of the American College of Cardiology, Vol. 42, No. 8, pp. 1454-1462, 2003.

80% of patients had NYHA III symptoms despite this intensive background medical therapy confirms the severe nature of the underlying heart failure. Finally, the results of the study in both the control and treatment groups reflect the beneficial effects of this background therapy.

**Table 10: Baseline Cardiac Medications**

|                               | # Patients | % of 300 |
|-------------------------------|------------|----------|
| 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%    |

### **13. PRIMARY COMPOSITE ENDPOINT**

The primary endpoint was met with an odds ratio of 1.73 (p=0.024).

### **14. COMPONENTS OF PRIMARY ENDPOINT**

The composite endpoint had three independent components:

- Survival
- Major Cardiac Procedures
- Change in core lab NYHA class

**Figure 1** provides the Kaplan-Meier curve for survival. The number of patients at risk is listed at each time point. There were 25 deaths in each of the control and treatment groups. The Kaplan Meier curves demonstrate no difference in survival between the treatment and control groups ( $p=0.85$ ). However, mortality results were updated on 15 April 2005, yielding 33 deaths in control and 29 deaths in treatment ( $p=0.59$ ).

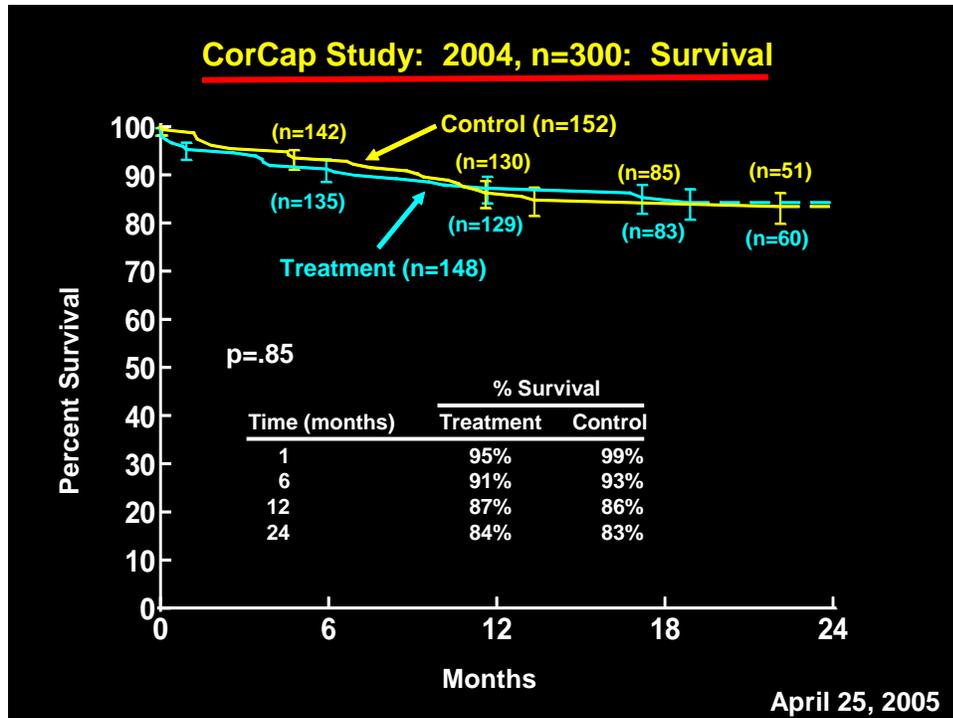


Figure 1: Survival

**Figure 2** illustrates the Kaplan-Meier curve for the endpoint of freedom from major cardiac procedure. The cumulative percent of patients free from a major cardiac procedure indicative of worsening heart failure was significantly lower in the control group through 24 months ( $p=0.01$ ).

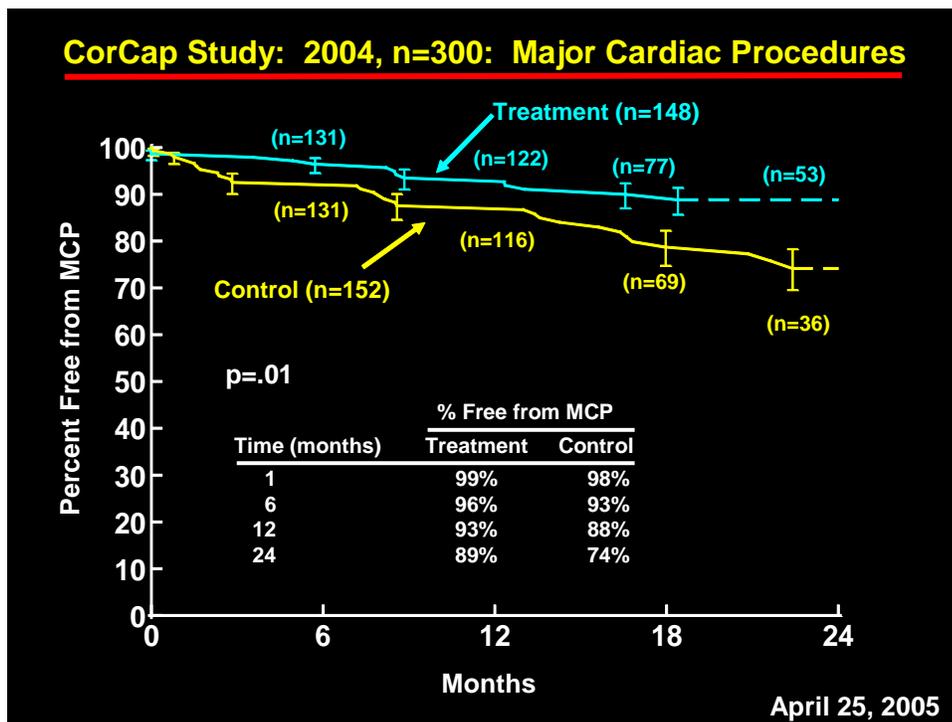


Figure 2: Freedom From Major Cardiac Procedure

**Table 11** contains analysis of NYHA using the following criteria (because of the interdependence of the components of the primary, these analysis criteria are necessary to get an accurate depiction of NYHA change without the influence of death or MCP):

- deaths are censored,
- VAD's and transplant are counted as NYHA IV,
- MCP's adjudicated by the CERC as worsening heart failure are counted as NYHA IV,
- MCP's adjudicated by the CERC as not worsening heart failure utilize the last NYHA classification prior to the MCP.

**Table 11: NYHA Component of the Primary Composite Endpoint**

|          | Treatment<br>(Average %) | Control<br>(Average %) | Odds Ratio<br>T/C<br>(95% CI) | p-value |
|----------|--------------------------|------------------------|-------------------------------|---------|
| Improved | 45.4                     | 33.0                   | 1.74 (1.00,<br>3.02)          | 0.049   |
| Same     | 36.0                     | 47.4                   |                               |         |
| Worsened | 18.6                     | 19.6                   |                               |         |

## 15. 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. A pre-determined success criterion combining these four major secondary endpoints using the Hochberg analysis was chosen. This success criterion was met (p=0.032) indicating patients structural and functional measures improved. **Table 12** summarizes the major secondary endpoints.

**Table 12: Major Secondary Endpoints**

| Major Secondary Endpoints | p-value |
|---------------------------|---------|
| LVEDV                     | 0.008   |
| LVEF                      | 0.49    |
| MLHF                      | 0.04    |
| NYHA (site)               | 0.60    |
| Hochberg Family-Wise      | 0.032   |

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## STRUCTURAL ENDPOINTS

Several structural endpoints were measured using an echocardiogram core lab. As summarized in **Table 13**, all structural endpoints favored the CorCap CSD. Four of the seven structural endpoints demonstrated statistically significant differences between the treatment and control groups. LVEDV, LVESV, sphericity and LVEDD indicated that the treatment patients had smaller, more elliptical shaped ventricles. Left ventricular mass index tended to be reduced consistent with reduced left ventricular hypertrophy.

**Table 13: Summary of Cardiac Structural Endpoints**

| Structural Endpoints | Treatment Difference (T-C) | p-value |
|----------------------|----------------------------|---------|
| LVEDV                | -17.9 ml                   | 0.008   |
| LVESV                | -15.2 ml                   | 0.02    |
| LVEF                 | 0.83                       | 0.49    |
| Sphericity Index     | 0.042                      | 0.031   |
| Mass Index           | -5.9g/m <sup>2</sup>       | 0.15    |
| LVEDD                | -1.8 mm                    | 0.02    |
| LVESD                | -1.2 mm                    | 0.21    |

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**T FUNCTIONAL ENDPOINTS**

Several quality of life and exercise performance tests were also conducted to measure patient functional status. As summarized in **Table 14**, treatment patients had a better quality of life than the control patients as assessed by two different instruments (MLHF and SF-36). Although there was a large amount of data missing for cause (e.g., patients sicker or hospitalized) in the control group, rank order tests for 6-minute walk and peak VO<sub>2</sub> favored treatment.

**Table 14: Summary of Functional Endpoint**

| Functional Endpoints           | Treatment Difference (T- C) or Odds Ratio | p-value |
|--------------------------------|---|---------|
| MLHF                           | -4.47                                     | 0.04    |
| SF-36 General Health Domain    | 9.13                                      | <0.0001 |
| SF-36 Physical Function Domain | 5.41                                      | 0.015   |
| NYHA (Site-assessed)           | -0.04                                     | 0.60    |
| 6-minute Walk Distance         | 1.27 (Odds Ratio)                         | 0.24    |
| Peak VO <sub>2</sub>           | 1.37 (Odds Ratio)                         | 0.15    |

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**CONDARY ENDPOINTS**

**Table 15** summarizes the other secondary endpoints measured in the trial. The length of stay for re-hospitalizations favored treatment (p=0.19). Per analysis

previously presented in this summary, the change in core lab NYHA (censored for death and VAD's, transplants, and MCPs adjudicated by the CERC as worsening heart failure counted as NYHA IV) was significant (p=0.049). The control group had a larger decrease in BNP than the treatment group which was significant (p=0.014). This was not surprising since the baseline BNP values for both groups were in the "normal or less than 100" range (patients were well managed on their heart failure medications and stable enough to undergo cardiac surgery).

**Table 15: Other Secondary Endpoints**

| Other Secondary Endpoints            | T                 | C   | p-value      |
|--------------------------------------|-------------------|-----|--------------|
| Median Re-hospitalization LOS (days) | 3.0               | 4.0 | 0.19         |
| Mean Re-hospitalization LOS (days)   | 5.8               | 9.9 |              |
| Core Assessed NYHA                   | 1.74 (odds ratio) |     | <b>0.049</b> |
| BNP                                  | 77.33 (T-C)       |     | 0.014        |

## **19. ANALYSIS OF STUDY AND RISK/BENEFIT ASSESSMENT**

The safety and efficacy results presented in this PMA application indicate that the CorCap CSD is safe and effective for its Intended Use. This conclusion is based on a benefit-risk assessment characterized by the following factors defined in 21 CFR 860.7:

### **Well-Controlled Clinical Investigation**

The CorCap CSD clinical trial, “*Clinical Evaluation of Acorn Cardiac Support Device Therapy in Patients with Dilated Cardiomyopathy*,” clearly meets FDA’s definition of a well-controlled clinical investigation. The objectives of the study, the methods for patient selection, the data procurement methods, the study design (including the use of an active treatment control), and the analysis methods all meet or exceed FDA criteria. Additionally, the CorCap CSD was standardized in its design and performance throughout the trial.

### **Valid Scientific Evidence**

The safety and efficacy results presented in this PMA application are derived from a well-controlled clinical investigation and, therefore, meet FDA’s definition of Valid Scientific Evidence. As such, qualified experts will be able to fairly and responsibly evaluate whether the CorCap CSD is safe and effective for its Intended Use.

### **Reliability of the CorCap CSD**

There were no reliability issues associated with the CorCap CSD during its IDE clinical investigation or per its commercial use in the EU. The CorCap CSD has proven to be consistent in its design, method of delivery, and performance. There have been no deaths or AE’s related to the CorCap CSD. Further, Acorn has not received any user complaints regarding the CorCap CSD. Finally, there were no Serious Unexpected Adverse Events in the CorCap CSD IDE trial, and there have been no Vigilance reports associated with its usage in the EU.

## **Efficacy**

The Valid Scientific Evidence presented in this PMA application provides reasonable assurance that the CorCap CSD (per its intended use and instructions for use) is efficacious in a significant portion of its target population as evidenced by the clinically significant results. The basis for this assertion is as follows:

- The CorCap CSD IDE study met study objectives.
- The primary objective of the study showed that the CorCap CSD improved patient functional status as measured by a clinical composite consisting of mortality, major cardiac procedures, and change in NYHA functional class (p=0.024).
- When analyzed by stratum, the odds-ratios achieved for the clinical composite were directionally similar to the all-patient cohort, demonstrating similar treatment effect.
- The secondary objective of the study showed that the CorCap CSD improved a combination of patient functional status and LV structural parameters as measured by meeting a Hochberg success criterion for LVEDV, LVEF, MLHF, and NYHA (p=0.032).
- The CorCap CSD significantly improved structural and functional endpoints as experienced by: reduction in LVEDV (p=0.008), reduction in LVESV (p=0.02), change to a more elliptical shape (p=0.031), reduction in LVEDD (p=0.02), improvement in MLHF (p=0.04), improvement in SF-36 (SF-36GH: p<0.0001 and SF-36PF: p= 0.015) and improvement in core lab NYHA (p=0.049).
- In addition to the statistical significance demonstrated by the primary and secondary objectives of the study, the CorCap CSD demonstrated clinically significant results as demonstrated by the treatment difference in both the primary and secondary endpoints.
- Furthermore, clinical significance of the secondary study objectives is bolstered by the statistically significant correlations between cardiac structural and patient functional endpoints.
- The pre-clinical studies and human safety studies conducted by Acorn demonstrate treatment results consistent with the efficacy results in the CorCap CSD IDE study.
- There is an unmet need in heart failure for a therapy to treat LV dilation.

## **Safety**

Since the probable benefits from the CorCap CSD (when used per its Indications for Use and Instructions for Use) outweigh any probable risks as demonstrated by Valid Scientific Evidence, there is reasonable assurance that the CorCap CSD is safe. The basis for this assertion is as follows:

- The CorCap CSD showed a non-significant mortality difference as measured against control ( $p=0.85$ ). (*Note: updated results on 15 April 2005 showed 29 deaths in treatment and 33 deaths in control which yielded a p-value of 0.59*).
- The CorCap CSD demonstrated a non-significant difference in serious adverse events as measured against control ( $p=0.43$ ) (*note: updated results on 15 April 2005 yielded a p-value of  $p=0.33$* ).
- The CorCap CSD demonstrated a non-significant difference in the combination of death or serious adverse events as measured against control ( $p=0.18$ ).
- The CorCap CSD significantly reduced Major Cardiac Procedures indicated for worsening heart failure as measured against control ( $p=0.01$ ).
- Risk associated with the design, delivery, and performance of the CorCap CSD was successfully analyzed through a Risk Management process and mitigated through Acorn's physician training program and labeling for the CorCap CSD.

**J. Panel Recommendations (To be completed by FDA)**

**K. CDRH Decision (To be completed by FDA)**

**L. Approval Specifications (To be completed by FDA)**