

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

EXECUTIVE SUMMARY

PUBLIC HEALTH NEED

- Heart failure remains one of the most important public health problems in the United States. It has been estimated that heart failure affects 5 million patients and results in an economic burden of almost 30 billion dollars each year.¹ Current therapies for New York Heart Association (NYHA) Class II-IV patients, such as medical management with drugs, coronary artery bypass grafting (CABG), mitral valve repair, and bi-ventricular pacemakers, have limitations and none specifically address cardiac remodeling, which is a fundamental pathophysiologic mechanism of heart failure.

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 device can constrain an end-diastolic design pressure of 50 mm Hg for in-excess of twenty-five years. 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).
- The proposed **Indication for Use** is:

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 left ventricular ejection fraction (LVEF) $\leq 35\%$ (or LVEF $\leq 45\%$ if mitral valve repair or replacement is planned).

NON-CLINICAL STUDIES

- **Proof of concept studies performed in three independent animal models of heart failure showed consistent effects of the CorCap CSD to reduce LV size and improve LV function.**
 - In a dog model of heart failure, animals that received the CorCap CSD demonstrated a significant decrease in LVEDV ($p < 0.05$) and an increase in LVEF ($p < 0.05$).²
 - In a dog model of heart failure, animals that received the CorCap CSD had improved cardiomyocyte contraction and relaxation, down-regulation of stretch response proteins, and increased affinity of the pump for calcium.³
 - In an ovine model of heart failure, the CorCap CSD implant maintained or reduced heart size and increased LVEF, fractional shortening and peak positive dP/dt.⁴
 - In sheep with heart failure produced by ligation of coronary arteries, thus causing only mild dilation, consistent findings of reduced ventricular size and improved ventricular function were also reported.⁵
- Laboratory studies have been conducted to evaluate and understand the mechanism of action of the effects of the CorCap on myocardial cell structure and function, histology, biochemistry and molecular gene products.

SAFETY 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. No serious adverse events or deaths were reported as device-related.
 - These patients showed significant improvement in cardiac structure and function, which was associated with a significant improvement in NYHA functional class and quality of life measures.
 - An additional 85 patients 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.

BRIEF REGULATORY BACKGROUND AND CONTEXT

- The pivotal trial for the CorCap CSD was designed in close collaboration with the Food and Drug Administration (FDA).
- FDA granted approval to conduct a feasibility study in November 1999. In June 2001, Acorn received unconditional approval to expand the trial (170 patients) to the pivotal phase, eventually expanded to 300 patients total.
- **To meet FDA’s requirement for an unbiased NYHA assessment as part of the primary composite endpoint, a blinded methodology for assessing NYHA at baseline by a core lab was implemented after the study was initiated.** As a result, 174 subjects enrolled prior to the new core lab assessment protocol did not have a core lab NYHA classification at baseline. All patients had core lab NYHA classification at final follow-up visit.
- **FDA recommended that multiple imputation methodology be used to impute missing baseline NYHA core lab data, and rejected Acorn’s alternative proposals for analyzing NYHA data.**⁷ FDA’s letter of May 29, 2004 to Acorn states: “For primary analyses, it is not acceptable to use two unblinded assessments or to use one blinded and one unblinded assessment.”
- The Circulatory System Devices Advisory Panel convened in June 2005 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. For the reasons explained below, this Panel’s deliberations were not fully informed because the members lacked information about the statistical imputation methodology and misunderstood the facts about missing data (see next section). In addition, this Panel was held prior to amendment of the PMA, and thus they lacked the new data that is now before this MDDRP.
- FDA issued a not-approvable letter for the CorCap CSD PMA in August 2005 citing: three safety concerns (peri-operative death, safety of re-operation due to adhesions, long-term pericardial constriction) and three effectiveness concerns (missing data for the primary endpoint, lack of statistical significance in secondary endpoints, absence of a specific patient population in which the device appears effective).
- **In response to one of three options offered by FDA to place the PMA in approvable form, Acorn amended the PMA to identify a cohort of patients from the pivotal trial with a greater benefit-risk ratio.** This “focused cohort” analysis, developed with the clinical trial investigators, provided a basis for modification of the indication for use to eliminate patients who have: indexed left ventricular end

- diastolic dimension $<30 \text{ mm/m}^2$ or $>40 \text{ mm/m}^2$ and LVEF $\geq 35\%$ (or $\geq 45\%$ if planned mitral valve repair or replacement), despite optimal medical management.
- FDA issued a not-approvable letter for the amended PMA. **Although FDA’s first not-approvable letter had listed a post-hoc analysis to identify a sub-group at lower risk as one of the available methods to address the agency’s concerns, FDA’s second not-approvable letter rejected that approach.** FDA then 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. FDA’s second not-approvable letter failed to contain an explanation of the specific reasons for the disapproval as required by the regulations at 21 CFR 814.44(f).
 - FDA subsequently agreed that the method applied by Acorn to handle missing data at baseline is statistically valid and appropriate:

“After further analysis, FDA believes that Acorn’s primary endpoint analysis is robust and that technical questions about the imputation methods are now a secondary concern.”⁸
 - **Acorn believes the PMA establishes reasonable assurance of safety and effectiveness, as defined by regulations and precedent, and the sound science provided in the submission.**
 - The pivotal trial was a well-controlled randomized investigation of 300 patients at 31 sites.
 - The protocol-specifiedⁱ success criterion for the primary endpoint was met.
 - The protocol-specified success criterion for the secondary endpoints was met.
 - The primary endpoint evaluated clinically relevant outcomes for heart failure patients (functional status, disease progression, mortality).
 - An additional 119 patients treated with the CorCap in safety and surveillance studies in Germany, Australia, and other OUS locations did not identify any previously unknown risks. Efficacy signals were consistent with the results seen in the safety studies.

ⁱ “Protocol-specified” refers to protocol Revision 8, as submitted in the PMA.

THE DELIBERATIONS AND DECISION OF THE PREVIOUS PANEL WERE INADEQUATELY INFORMED

- The Division of Cardiovascular Devices (DCD) proposes to include in their Panel Pack the transcript and DVD of the June 22, 2005 Circulatory System Devices Advisory Panel meeting for review by the MDDRP members. For this reason, Acorn will summarize below the reasons why the deliberations and determinations of the prior Panel were inadequately informed and thus should not be taken into account in this MDDRP proceeding.
- Significant flaws in the Panel process are summarized below:
 - The Panel misunderstood the reason for the ‘missing’ baseline core lab NYHA data, and did not have an accurate understanding of how much data was missing.
 - The imputation method used by Acorn to handle this missing data was recommended by DCD, but it was not provided to the Panel in advance of their meeting. Because of this, the statistician member of the Advisory Panel stated that she was unable to provide meaningful expert comment to her colleagues on this topic.
 - DCD presented observations included in operative reports of adhesions observed following CorCap implantation, which some Panel members interpreted as representing a problem in the treatment arm of the trial, when in fact adhesions were observed in both arms. The physician who authored one of these operative reports (Dr. Patrick McCarthy) subsequently wrote a letter to DCD objecting to his statements being taken out of context, and expressing his support for the safety and effectiveness of the CorCap CSD. This letter is included as an attachment to the Clinical Study Summary.

CLINICAL STUDY DESIGN

- The CorCap CSD pivotal study was a multi-center, prospective, stratified and randomized, controlled evaluation of 300 patients with heart failure.
- **The study constituted one of the largest controlled studies involving a permanent device implant and cardiac surgery in patients with heart failure.**
- The study was designed to test the hypothesis that the CorCap CSD will improve patient functional status as measured by a clinical composite endpoint consisting of mortality, major cardiac procedures indicative of progressive heart failure (heart transplantation, VAD placement, CABG, biventricular pacing device, or subsequent MVR or TVR) and change in NYHA functional classification.
- Design features were implemented to reduce the potential for bias that can accompany surgical trials. These included blinded core labs, an independent Clinical

Events Review Committee (CERC), an independent Data Safety Monitoring Board (DSMB), and blinding of Acorn and the investigators to the aggregate results.

CLINICAL STUDY RESULTS

- **The pivotal clinical trial of the CorCap CSD met all protocol-specified criteria for success.**
- 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.

Effectiveness

- **The study met its primary composite endpoint (p=0.024).** The imputation methods utilized to account for the missing baseline core lab NYHA classification data in some subjects were appropriate, as verified by independent outside experts and confirmed by FDA. All sensitivity analyses of the imputation methodology demonstrated the robustness and validity of the methodology.
 - The focused cohort demonstrated an even greater improvement in the primary endpoint in the CorCap CSD group (p=0.011).
- **An analysis of four major secondary endpoints (LVEDV, LVEF, MLHF and NYHA classification/site) achieved its protocol-specified success criterion (p=0.032).** The study also showed significant improvements in the CorCap group for many secondary endpoints (functional endpoints (MLHF, SF-36) and structural endpoints (LVEDV, LVESV, Sphericity, LVEDD)), which are supportive of the primary endpoint results.
- These results demonstrate a clinically significant benefit of the CorCap CSD.

Safety

- The CorCap CSD demonstrated an acceptable risk profile in the pivotal clinical study when compared to the expected benefit of the device.
- **At 12 and 24 months, the mortality rates were comparable in the treatment and control groups (12 months: 12.8% vs. 13.8%; 24 months: 16.9% vs. 21.7%) as of the December 2005 update.**
 - None of the reported deaths were adjudicated as device-related.
 - At 30 days post-op, there were 6 deaths in the treatment group (6/139 = 4.3%) compared to 1 death in the control group (1/102 = 1.0%). The rate observed in

- the treatment group is low and consistent with published databases for patients undergoing mitral valve repair or replacement.
- 30-day mortality was not different between treatment and control groups in the Focused Cohort population (1.3% treatment vs. 1.2% control).
 - 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).
- **The number of patients and type of AEs experienced were not different between the treatment and control groups.**
 - Overall, 81% of patients in the control group and 85% of patients in the treatment group had a reportable adverse event (AE). No device-related AEs were reported in this study.
 - As updated on April 15, 2005, 83.1% of the CorCap group had experienced any serious adverse event compared to 78.9% of the control group. The total number of patients that experienced a serious adverse event was not statistically different between the treatment and control groups.
 - **The treatment group experienced a 34% reduction in major cardiac procedures (p=0.01).**
 - There was no acute or long-term clinical evidence of pericardial constriction resulting from the CorCap CSD.
 - There is no evidence of increased morbidity or mortality due to adhesions in patients who undergo re-operation after CorCap implant.

Additional Analyses

- Study results were analyzed by whether patients underwent mitral valve repair / replacement or not. In general, sample sizes were not large enough to detect statistically significant differences in these subgroups.
 - The CorCap group showed improvements over control in the primary endpoint in both strata (No MVR: odds ratio=2.57 (p=0.032); MVR: odds ratio=1.51 (p=0.17)).
 - In the No MVR and MVR strata, overall trial results were not different between treatment groups through 24 months.

CONCLUSIONS

- **The CorCap CSD original PMA provides valid scientific evidence to support a determination that the product is safe and effective for its intended uses.**
- In addition, the PMA as amended as of December 2005 provided more information to FDA on a focused cohort of patients in the pivotal trial for which the benefit-risk ratio of the device was enhanced. FDA's six issues, as identified in the August 12, 2005 not approvable letter, have been addressed by Acorn in the amended PMA.
- **The three safety issues raised by the FDA have been adequately addressed by the sponsor:**
 - The risk of peri-operative death was reduced through physician training and labeling as demonstrated in the pivotal study, and was significantly reduced in the Focused Cohort population.
 - There was no acute or long-term clinical evidence of pericardial constriction resulting from the CorCap CSD. Patients in the study will be monitored for 5 years for any evidence of constrictive physiology. FDA has agreed that, given the nature of pericardial constriction, it is more appropriate to monitor for constrictive physiology in the post-market setting.⁹
 - Adhesions can occur after CorCap implantation, as with any surgery. This was not associated with any additional risk or adverse outcomes at re-operation in the clinical study. In addition, the proposed surgeon training program emphasizes appropriate patient selection and operative technique for subsequent surgery, and proposed product labeling specifically addresses issues related to risk reduction in reoperation following CorCap implantation.
- **Independent clinical and statistical experts have reviewed the data and information in the PMA and have concluded that the CorCap CSD demonstrated clinically meaningful and statistically significant improvements in the protocol-specified primary and secondary endpoints.** The protocol-specified statistical methodology utilized to generate these results was appropriate, well-executed, and scientifically valid. The CorCap demonstrates an acceptable safety profile when compared to the expected benefit of the device.
- Follow-up of patients in the pivotal trial continues; Acorn will continue to provide long-term follow-up to FDA and the clinical community post-approval.

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