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

FDA REVIEW MEMORANDUM – 23 MAY 2005
CORRECTIONS AND CLARIFICATIONS*

MEMORANDUM OF REVIEW

FROM: Michael R. Berman
TO: File, P040049
DATE: 23 May 2005
REF: Acorn Cardiovascular, Inc.
Cardiac Support Device (CSD)
A mesh bag intended for permanent implant around the heart of CHF patients to restrain further cardiac dilatation.
Panel pack summary review memorandum

FDA SUMMARY MEMORANDUM

INTRODUCTION

This memorandum summarizes the several pre-clinical, clinical and statistical memoranda generated during FDA's review of P040049 – the marketing application for the Acorn Cardiovascular, Inc. CorCap™ Cardiac Support Device (CSD). The device is a passive polyester mesh wrap that is placed around both ventricles of the heart; the intention is to inhibit further dilatation of the ventricles and thus to facilitate reverse remodeling of the myocardium. The CorCap™ CSD is indicated for use in adult patients diagnosed with dilated cardiomyopathy who are symptomatic in spite of optimal medical therapy. The CorCap™ CSD can be used alone or in conjunction with mitral valve repair or replacement, if the later therapy is judged appropriate.

Chronology

CHRONOLOGY	
Date	Event
10/25/99	IDE G990267 received; this is the IDE under which the clinical trial for the Acorn CorCap CSD was conducted.
11/24/99	Feasibility clinical trial approved
6/8/01	Pivotal clinical trial approved. Clinical protocol evolved during the trial; final protocol was Rev 8.

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* **Acorn's corrections and clarifications are directly inserted in bold text in the body of the memorandum.**

CHRONOLOGY	
6/19/02	**Acorn's Comment: Unconditional approval of Revision 6 of the protocol; this revision was based upon negotiations with and requirements imposed by FDA. Key changes included a new primary endpoint, increased sample size (from 170 to 300 patients), change to core lab NYHA protocol, and increase of follow-up from 6 to 12 months.**
6/12/03	Modular PMA process begins with approval of shell. M030010 contains 6 modules; PMA will begin with submission of module 6, the clinical module.
12/20/04	Clinical module submitted; P040049 begins.
12/29/04 – 3/25/05	Interaction with sponsor *via* email and telephone.
4/29/05	Major deficiency letter issued.
5/3/05	Amendment A001 – compilation of sponsor responses to FDA queries over the period 12/29/04 to 5/2/05. This material includes, but is not limited to, material provided by sponsor dated 1/13/05 and 3/25/05.
5/17/05	Amendment A002 – Sponsor response to major deficiency letter issued 4/29/05. This amendment also contained up-dated information as required by 21 CFR 814.20(e) and corrections and additions to the PMA.
5/19/05	Amendment A003 – sponsor's portion of Panel Pack.
6/22/05	Scheduled for review by Circulatory System Devices Panel

FDA REVIEW TEAM	
Lead reviewer	Michael R. Berman, Ph.D.
Clinical	Ileana L. Piña, M.D. and Julie Swain, M.D.
Statistics	Laura Thompson, Ph.D.
Engineering	Eric Chen, M.S. and Keith Foy, M.S.
Animal studies	William Riemenschneider
Biocompatibility	Keith Foy, M.S.
Sterilization and packaging	Sharon Lappalainen
Human factors and labeling	Walter Scott, Ph.D.
Manufacturing	Dolores Bernato
Post-market study design	Brock Hefflin, M.D.

Engineering (Module3)

The CorCap™ CSD device is a passive polyester mesh intended for permanent implant around both ventricles. The device system includes various tools to be used during device implant; none of these tools are themselves implanted. Some of the tools are for one-time use, others can be re-used and can be sterilized at the medical facility. The two-dimensional stress strain characteristics of the mesh were documented, as was the durability of the mesh under cyclical loading. Minor engineering concerns were identified and have since been adequately resolved. There are no remaining engineering concerns.

Animal Studies (Module 2)
No remaining concerns – this module was closed on 9/23/04.

Biocompatibility (Module1)
No remaining concerns – this module was closed on 8/30/04.
Sterilization and Packaging (Module4)
No remaining concerns – this module was closed on 10/15/04.

Manufacturing (Module 5)
No remaining concerns – this module was closed on 8/30/04.

CLINICAL (Module 6)

The CorCap is a permanently implanted device that is placed over the ventricles for patients with heart failure to attempt to impact on further ventricular dilatation and ventricular remodeling. The intended use is "to support the heart, in order to prevent further dilation that is associated with progressive heart failure, resulting in preserved or improved patient functional status."

The Trial:

I. Overall: The Acorn Trial was a prospective, randomized controlled, 4-arm study of heart failure patients either with mitral insufficiency requiring MVR or without mitral insufficiency.

A. Hypothesis: The CorCap would improve patient functional status as measured by a clinical composite consisting of mortality, major cardiac procedure for worsening heart failure (MCP), and change in NYHA Class.

B. Primary Objective: To compare the functional status after a minimum of 12 months of follow-up for patients randomly assigned to Treatment (CorCap) or Control (no CorCap).

C. Secondary Objective:
- To determine the rate of death and other SAE's experienced by patients randomized to CorCap 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.

II. Primary Composite Efficacy Endpoint: The study has a composite endpoint of all-cause mortality, NYHA class as per core lab, and Major Cardiac Procedures (MCP) indicative of progression of HF.

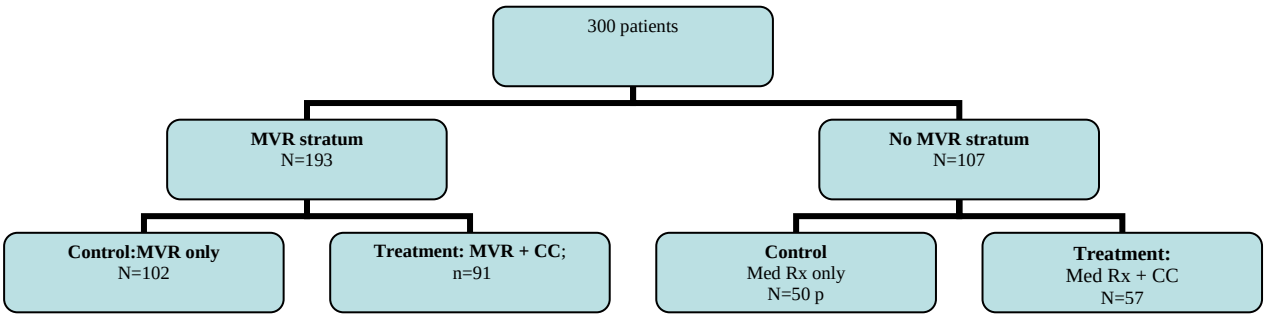
Secondary Efficacy Endpoints:
- Cardiac structure and function: reduction in LV size, LV function and re-shape of the LV
- Patient functional status: Improvement in QOL at 6 and 12 months (MLWHF, SF36), exercise status 6 and 12 months (6 min walk, CPX testing) and site-determined NYHA
- Changes in CPX , Peak VO2, ventilatory threshold, and exercise time at 6 and 12 months
- Changes in BNP
- All cause mortality and hospitalizations

- Incidence of MCP
- Safety: hospitalization, adverse events, major cardiac procedures and mortality
- # of hospitalizations, hospital days and ICU days

III. Patient Inclusion and Exclusion Criteria

- Refer to pages 15-17 in the Clinical Summary tab in the Panel Pack.

IV. Randomization: Table 1



Seven patients refused surgery, 2 died prior to the surgery, all from the treatment arms. Three patients in the CorCap group died shortly after surgery. The following table shows the patient distribution at sites by MVR vs. NoMVR stratum.

Table 2: Number of Patients by Stratum

	MVR	NOMVR
Large sites (5) > 16 pts	86	30
Medium sites (7) 11-16	53	46
Small sites (17) <=10	54	31

Baseline Characteristics; Only 10% of patients enrolled had an ischemic etiology as shown in the table below. However, the most common etiology of HF in the U.S. is ischemic cardiomyopathy…

> **Acorn's Comment: The study allowed dilated cardiomyopathy of ischemic or non-ischemic origin. However, candidates for surgical revascularization were excluded due to the inherent difficulty of defining a surgical revascularization control group and the inherent power issue associated with additional subgroups.**

…In addition, the VO_2 mean at baseline is higher than would be expected for this sick population especially with 40% women whose normal VO_2 is lower than that of men. The expected or predicted VO_2 for a 53 year old woman, 5'10" and 130 lbs is 22.5 ml/min/kg. A VO_2 of 15 ml/min/kg for such a patient is >50% of the predicted value (for her age and gender in the absence of disease), which indicates a reasonable 1 year prognosis.

The MLWHF score of 59.3 is only slightly worse than that of the A-HeFT trial which was 51 and enrolled over 90% NYHA Class III patients.

Table 3: Patient Characteristics

Parameter	Value
Age	52.5 years
Men	55.3%
Caucasian	65%
Etiology : Ischemic	10%
Non-ischemic (dilated)	81.6%
Valvular	11.3%
EF	27.4%
LVEDD	7.2 cm
Peak VO2	15.0 ml/min/kg
6 min walk	340.9 m
MLWHF	59.3

V. Medications:

Ninety-seven percent of patients were on an ACE Inhibitors or an Angiotensin II receptor blocker; 85.3% of patients were on beta blockers.

Doses of medications were not provided by the Sponsor. Types of medications alone do not constitute a well-medicated population. Doses of drugs should be given as proof of maximal medical therapy by evidenced-based guidelines. For example, a beta blocker may be administered and would count as "background therapy" but be kept at low doses which does not constitute "maximal therapy".

Acorn's Comment: Dosage amounts vary on a patient-by-patient basis and the proper "maximal dose" for one patient may not be the same for another.

VI. Follow-up:

Of 300 patients enrolled and 148 allocated to Treatment and 152 allocated to Control, only 1 patient in the control group had an unknown vital status. Twenty-five patients in each group expired during follow-up.

VII. Protocol Deviations:

Six patients did not meet the eligibility criteria; 11 patients had unstable medications within 30 days of enrollment, 5 patients were not on a diuretic or an ACE inhibitor.

Missing tests occurred in 47% of patients…

Acorn's Comment: Over the course of follow-up, a given patient would be expected to complete over 30 tests. "Missing tests" as referenced here includes any single test missed for any reason, including tests that did not contribute to primary or secondary endpoints.

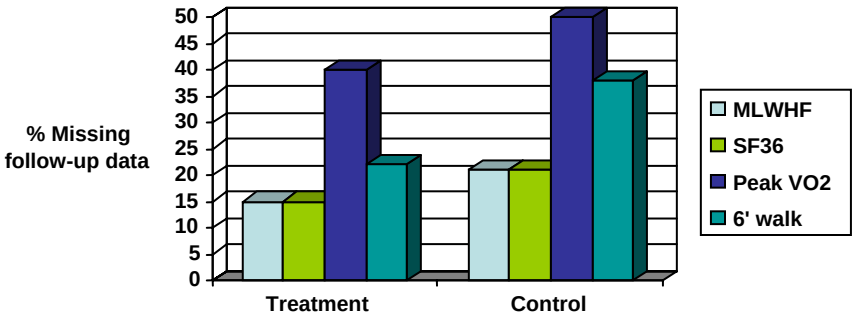
…In the Treatment arm, 59% of patients did not have a baseline CoreLab NYHA assessment. In the Control arm, 57% of the patients did not have a baseline CoreLab NYHA assessment.

In addition, there were missing data for VO_2 and 6-min walk as well as for MLWHF at 12 months follow-up…

Acorn's Comment: It is important to consider in any evaluation of missing data that missing 6MW and Peak VO_2 data were missing for cause and not missing at random.

…The following graph depicts the missing follow-up data for various parameters in the Treatment and Control arms, respectively.

Graph 1: Missing Data



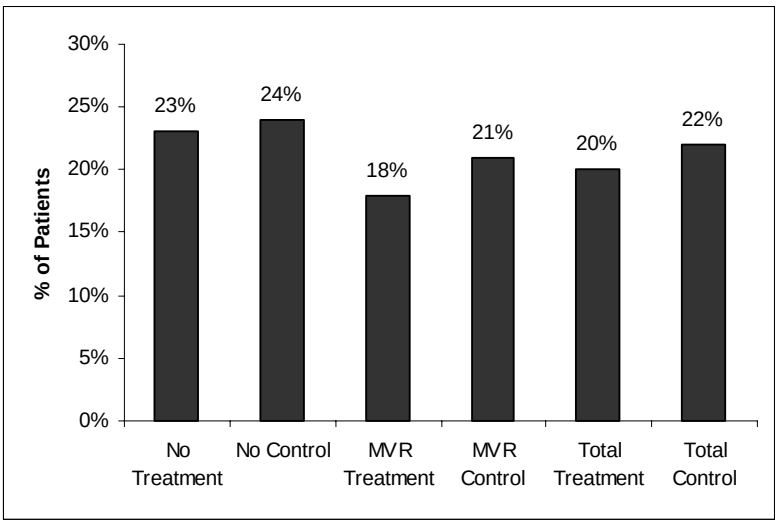
Acorn's Comment: Graph 1 depicts the calculation of percent missing based on an analysis of paired data at 12 months. Thus, it depicts an inflated number by displaying the fraction of patients who contributed baseline measurements but not 12 month measurements; specifically, patients who did not contribute 12 month data because they were dead were counted as missing in this graph. A more appropriate analysis for evaluating this type and volume of data is longitudinal regression analysis which uses all available data at all time points, and which does not include dead patients in calculation of missing data.

The statistical analysis of the primary effectiveness composite endpoint is presented below in the Statistics section of this summary memorandum.

VIII. Mortality

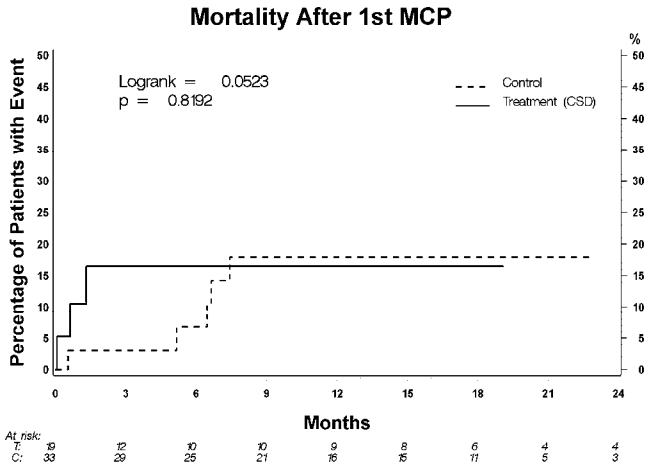
There was no significant difference in mortality as noted in the graphic below. Four deaths are attributed to surgery and the "up-front" cost of surgery. Using intent-to treat analysis, 7 patients in the Treatment group died within 30 days (including a patient who died prior to surgery) vs. 1 patient in the Control group. This graph is derived from the updated Sponsor information of April 15, 2005.

Graph 2: Mortality



There were 7 patients who died within the first 30 days of surgery in the Treatment group and 1 in the Control group. One patient of the 7 in the Treatment group died prior to surgery on the evening of randomization. Therefore, the true perioperative mortality is 4.3% in the Treatment arm. The following graph shows the mortality at 24 mos after the first MCP.

Graph 3



IX. Major Cardiac Procedures

Major Cardiac Procedures (MCP) were defined as surgical interventions for worsening heart failure. The table below relates to the MVR stratum only.

Table 4: MCP for MVR Stratum

	Treatment (n=91)			Control (n=102)			HR[&] (T/C) (95% CI)	p-value[+]
	# Pts	# Events	Rate*	# Pts	# Events	Rate*		
Cardiac Transplant	6	6	3.8	10	12	6.2	0.63 (0.23, 1.74)	0.37
LVAD	3	3	1.9	6	7	3.6	0.57 (0.14, 2.28)	0.43
MVR	1	1	0.6	3	3	1.8	NA	NA
Bi-Ventricular Pacing	6	6	3.8	7	8	4.3	0.75 (0.24, 2.36)	0.62
TVR	0	0	0.0	2	2	1.2	NA	NA
Any of above procedures	14	16	9.3	21	32	14.2	0.57 (0.28, 1.16)	0.12

*Rates are per 100 patient-years.
+p-value for comparison of time to first event (HR=1).
[&]HR is hazard ratio, treatment:control.

Table 5: MCP for NoMVR Stratum

	Control			Treatment			
	# Pts	# Events	Rate	# Pts	# Events	Rate	p-value
Cardiac Transplant	6	6	7.5	1	1	1.1	0.06
LVAD	2	2	2.4	0	0	0	NA
MVR	0	0	0	0	0	0	NA
Bi-Ventricular Pacing	7	8	9.2	4	4	4	0.24
TVR	0	0	0	0	0	0	NA
Any of above procedures	12	16	16.8	5	5	5.8	0.03

FDA has raised the question of treatment bias in this unblinded study; that is, whether surgeons, cardiologists, and patients have a different threshold for re-operations than for first-time cardiac operations. Statements in the operative reports indicate extreme difficulty was encountered in reoperating on some patients who had the CorCap device implanted for several months, which may indicate a treatment bias resulting in reduced cardiac surgical procedures in the Treatment group. Post operative days in the hospital are similar between the Treatment and Control arms. Time on cardiopulmonary bypass (pump time) was not available for all patients. For patients who had reoperations, the pump time was less in the Control patients than in the Treatment patients (153.75 minutes (n=8) vs.186.2 minutes (n=7).

Acorn's Comment: This analysis includes only MVR treatment patients and combines the CPB times for transplant, VAD, and MVR/TVR reoperations. The appropriate analysis should include all patients who had a baseline and subsequent

reoperation > 30 days after initial procedure, and should compare CPB times for transplant patients only. In that case, the pump time for Control patients was 193 minutes (range=128-284), similar to the pump time for the Treatment patients, which was 207 minutes (range = 158-270 minutes).

A Clinical Events Review Committee (CERC) adjudicated all MCP's in this trial. The Committee determined that of 41 MCP's reviewed, 9 were not associated with "worsening HF" and therefore are not counted as qualifying for "worsening" in the endpoint. Of the 9 MCP's 8 were in the Control Group and 1 in the Treatment Group. Of the 9 MCP's, 7 were BiV pacing implantation, 1 was mitral valve surgery and 1 was tricuspid valve surgery.

FDA has also reviewed the operative reports (by surgeons) of patients with MCP's and has concerns with the CERC's classification of worsening HF in several patients…

Acorn's Comment: The Clinical Events Review Committee was an independent body instituted to perform independent review of adverse events.

…The sponsor provided clinical summaries for 2 patients: 1 in the MVR Treatment arm and 1 in the MVR Control arm. Based upon the review of these summaries and the operative reports, FDA has concerns with the assessment of "worsening HF" which implies worsening LV function for the following reasons:

- One MVR Treatment patient and one MVR Control patient had mitral stenosis with significant valve gradients. One MVR Control patient needed to return to the OR months later for fungal endocarditis of the tricuspid valve. The sponsor has also provided clinical summary data on an additional 2 MVR Control patients who received cardiac transplants and a brief note on another MVR Control patient who expired prior to the end of study.
- Although the clinical summary on a patient in the MVR Control group states that "it seems unlikely that the transplant was due to a problem with the initial mitral valve procedure", the surgical report states that the "patient redeveloped severe MR from a tethering of the posterior leaflet." Therefore, in the opinion of the surgeon, the worsening HF was due to worsening MR from tethering of the posterior leaflet.
- The clinical summary provided states that post op a MVR Control patient suffered a pulmonary embolism followed by cardiogenic shock. The surgical report confirms this as well. Although the patient had "cardiogenic shock", this clinical presentation requiring another procedure (transplant) is not due to progressive HF.
- Another MVR Control patient had mitral valve and tricuspid valve repair. Two months later, the patient developed severe TR and was returned to the OR for tricuspid valve surgery.

A. Cardiac Resynchronization Therapy (CRT)

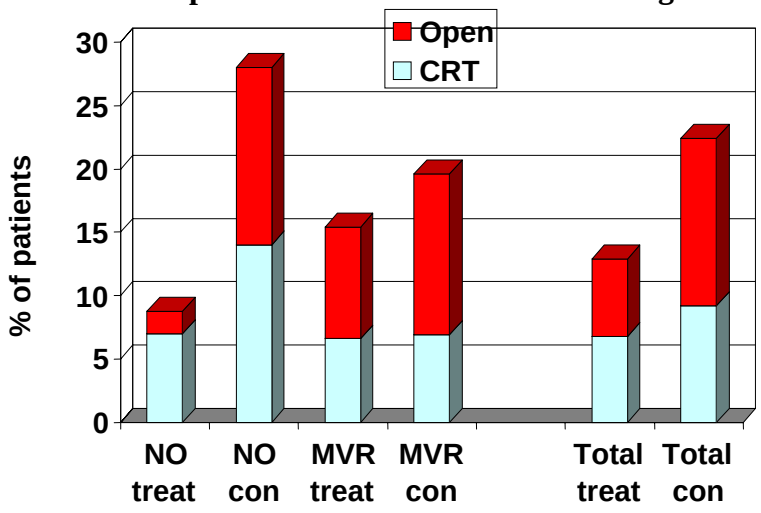
Cardiac Resynchronization Therapy (CRT) became available during this study. CRT insertion is presumably prompted by worsening heart failure, a QRS >120 msec, and appropriate maximized medical therapy. More patients received CRT in the control group (14 patients) than in the treatment group (10 patients). CRT could have been offered as concomitant therapy to patients who could not crossover to the treatment arm.

Below are the rates for CRT vs. open heart surgery. The graph below depicts the percent of CRT and open surgery by group.

Table 6: Rates for Pts Needing CRT vs Open Heart Surgery

	% patients needing CRT		% patients needing open-heart	
	CorCap	**Control**	**CorCap**	**Control**
No MVR	4/57=7%	7/50=14%	1/57=1.8%	7/50=14%
MVR	6/91=6.5%	7/102=6.9%	8/91=8.8%	13/102=12.7%
Total	10/148	14/152	9/148	20/152

Graph 4: Percent of Patients Receiving CRT



B. LVADS AND TRANSPLANTS

Transplants

Twenty three patients received a heart transplant: 6 patients in the MVR + CorCap group, 1 in the NoMVR CorCap Group, 10 in the MVR Control group and 6 in the NoMVR Control group. Of the 6 LVAD's in the MVR Control group, 4 were followed by a transplant during the follow-up period. One patient in the Treatment group had a subsequent transplant during the follow-up period.

In 19 of the 23 patients, the date of listing is after the date of randomization. Four patients were listed for transplant prior to randomization. Three of these patients, (all as Status II), were enrolled under the Revision 3 protocol which did not exclude patients on the transplant list. The fourth patient was considered UNOS Status 7 (inactive) at the time of enrollment. See Table below for the 4 patients.

Table 7: UNOS Status for 4 Pts Listed for Transplant Prior to Randomization

Group	noMVR Control		MVR Control	MVR Treatment
UNOS Status	Ib	II	II	Ib
Mos from enrollment transplant	8	13	6	9

Table 8: Timing of transplant for all patients who underwent transplantation.

	Treatment Assignment	Months to Listing*	Months from Listing to Trans.*	UNOS Status at Time of Transplant
1.	Treatment	5.78	0.36	Ia
2.	Control	5.78	1.38	Ia
3.	Control	8.44	5.95	Ia
4.	Control	8.80	8.02	Ib
5.	Control	19.45	2.53	Ib
6.	Control	-45.53	53.68	Ib
7.	Treatment	7.95	22.80	Ib
8.	Control	-27.46	34.79	II
9.	Control	6.44	7.82	Ib
10.	Control	0.36	1.12	Ib
11.	Control	22.14	~ 1	Ib
12.	Control	1.22	0.36	Ib
13.	Treatment	7.62	0.56	Ib
14.	Treatment	27.83	1.54	Ib
15.	Control	25.00	0.39	Ib
16.	Control	-0.59	13.57	II
17.	Treatment	8.15	0.69	Ia
18.	Control	-0.03	1.22	Ia
19.	Treatment	0.20	8.94	Ib
20.	Control	10.45	0.76	Ib
21.	Control	0.33	2.60	Ib
22.	Control	3.02	0.72	Ia
23.	Treatment	11.33	0.99	II

*Calculated by subtracting from the surgery date or enrollment date (if no surgery).

As per Sponsor, there were three patients (all MVR control) (2 MVR Controls and 1 MVR Treatment) who were listed within 30 days of their initial surgery. One of those 3 patients was classified as worsening HF and adjudicated as such. This was likely due to complications that occurred with the initial surgery. Excluding those 3 patients, the average time to transplant was 12.11 months.

Left Ventricular Assist Devices (LVADs)

None of the 11 patients who received an LVAD were listed for transplantation prior to enrollment. Six were listed prior to LVAD insertion as a bridge to transplant. Three patients were not on the transplant list and 2 were listed after the LVAD was placed. There were, therefore, 3 patients who received LVAD's that were never listed for transplant.

Of the 3 patients who received LVAD's but were never listed, 2 patients received LVAD's after initial surgery (1 MVR Treatment, 1 MVR Control) as complications of surgery. Of these 2 patients, one (MVR Treatment) recovered function and the LVAD was removed while the other although function improved (MVR Control), ultimately died of an arrest 4 months later. The third patient (MVR Treatment) developed an infection and could not go through surgery but deteriorated and received an LVAD and subsequently expired.

Table 9: Months to LVAD Placement and Death or Transplant Date

	Treatment Assign.	Mths to VAD*	Death Date	Transp. Date
1.	Control	0.07	16 Jul 02	N/A
2.	Treatment	0.00		22 Jul 03
3.	Control	8.51		11 May 03
4.	Treatment	3.55	16 Jul 03	N/A
5.	Control	20.43		28 Feb 04
6.	Treatment	0.00		N/A
7.	Control	2.30	22 Aug 02	N/A
8.	Control	1.48	27 May 02	N/A
9.	Control	0.66	10 May 02	10 May 02
10.	Control	0.79		11 May 03
11.	Control	7.75		N/A

*Calculated by subtracting from date of surgery or date of enrollment (if no surgery).

Three patients (two Treatment and one Control) were made Status 7 because of improvements in functional capacity. Both Treatment patients were subsequently transplanted.

Table 10: List of Patients Changed to Status 7

Patient ID	Treatment or Control	Enrollment Date	Transplant Listing Date	UNOS Status at Listing	Date of Change to UNOS Status 7	Date Re-Activated/UNOS Status	Date of Transplant/ UNOS Status
3301*	MVR +T	9 Jun 00	13 Feb 01	Ia	26 Jun 01	27 Nov 02/Ib	8 Jan 03/Ib
3325	No MVR +C	15 May 03	23 Aug 02	Ia	22 Jul 03	N/A	N/A
3952	MVR +T	16 May 02	7 May 02	II	28 Jun 02	14 Jan 03/II 28 Jan 03/Ib	3 Feb 03/Ib

*3301 had a bi-ventricular pacemaker on 2 Dec 02

In summary, there were MCP's that may have been prompted by a failed initial surgery. In addition, there are MCP's in patients who had other complications related to earlier surgery, and, in the opinion of the agency, may not be due to "worsening HF." At least 2 LVAD placements were related to surgical issues surrounding the first operation. Thus, the decision to have an MCP rests with each clinical center in charge of patient care. It is difficult to determine why some patients underwent a second surgical intervention, while others, who may have decompensated equally and had worsening NYHA Class, did not receive an MCP.

X. Functional Measures: In an unblinded trial, the possibility of placebo effect exists for NYHA assessments by patients and their physicians (including the data sent to the Core Lab for Core Lab determination of NYHA). Assessment of exercise (functional) capacity is less likely to be influenced by placebo effect and possibilities of bias.

A. NYHA Class

A core lab was instituted to assess NYHA independent of the site. Patients were classified as Improved, Same, or Worse for purposes of the composite primary effectiveness endpoint based, in part, on NYHA class. However, both baseline and 12

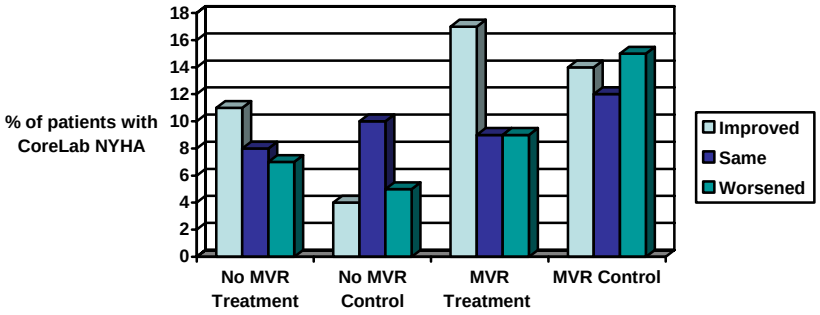
month core lab assessment was performed in only a subset (less than 50%) of the total patient group. The following Table shows the primary effectiveness classification of only those patients with baseline and 12 month NYHA class as assessed by the core lab.

Table 11: Primary Effectiveness Classification

	No MVR Treatment (n=26, 46%)	**No MVR Control (n=19, 38%)**	**MVR Treatment (n=35, 38%)**	**MVR Control (n=41, 40%)**
Improved	11	4	17	14
Same	8	10	9	12
Worsened	7	5	9	15

Graph 5

Acorn's Comment: This should be "Number (#) of Patients"

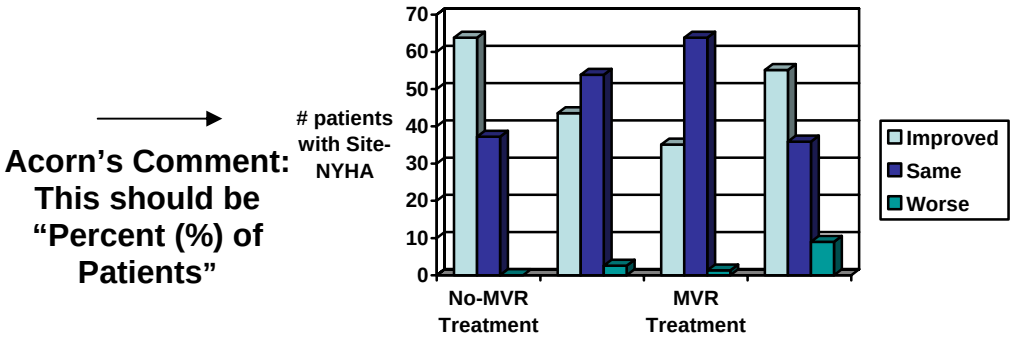


Using the site assessed NYHA Class for patients with both baseline and 12 month data, results are presented below. Improved 2+ or 1 have been grouped into "improved".

Table 12: Results Using Site Assessed NYHA

	NoMVR Treatment(n=43)	**NoMVR Control (n=39)**	**MVR Treatment (n=80)**	**MVR Control (n=78)**
Improved	27	17	28	43
Same	16	21	51	28
Worsened	0	1	1	7

Graph 6



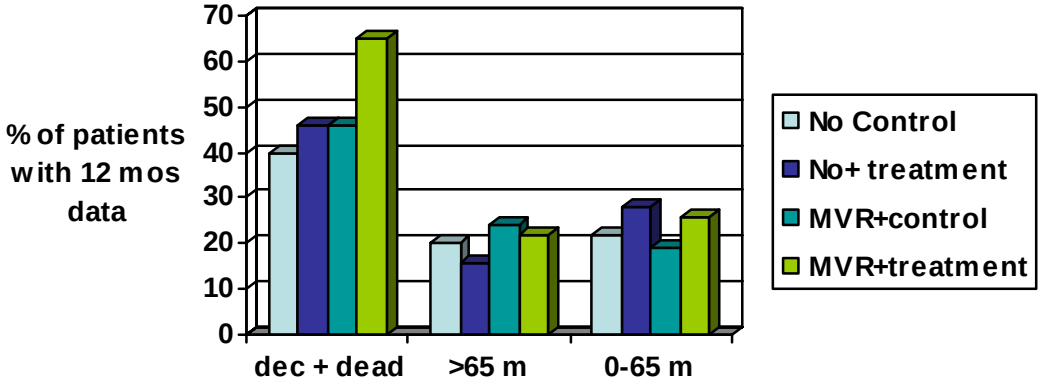
A greater number of patients improved in the no MVR treatment group than in the NoMVR control. A greater number of patients improved in the MVR Control vs. MVR Treatment and more patients were unchanged in the MVR treatment group vs. control.

B. Exercise (Functional Capacity)

In an unblinded trial, assessments of functional capacity, such as VO_2, are not as vulnerable to the placebo effect as are more subjective assessments of patient functional capacity. The lack of difference among groups in this more objective test (i.e., VO_2) differs from the effects seen in NYHA and QOL questionnaires. It should be noted, however, that there were more data missing in the Control than in the Treatment group. The lack of difference noted above is only among the patients whose data are remaining.

6 min walk:

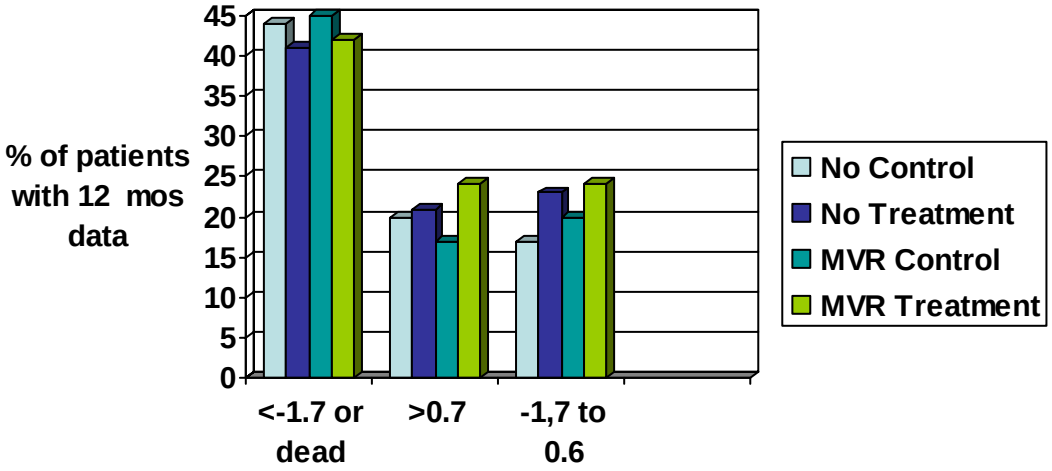
- 77 patients had no 6 min walk data
- In the **MVR stratum** group, 75/91 patients (82%) had data at baseline and 12 months in the treatment arm and 54/100 (54%) had data at baseline and 12 months in the control arm
- In the **NoMVR stratum**, 40/57 (70%) patients had data at baseline and 12 months in the treatment arm and 30/50 (60%) had data at baseline and 12 months in the control arm.
- The graph below divides the patients according to stratum and by changes in distance >65 m or 0-65 m or decrease. The patients who died and those who had an MCP within 12 months are included in the decreased group.



Cardiopulmonary exercise testing for peak VO_2

- At least one test was available in 74% of treatment patients and 62% of controls. 75/152 (49%) control patients had VO_2 data at baseline and 12 months follow-up and 90/148 (61%) treatment arm patients had baseline VO_2 and followup data.

- The following graph depicts the 12 month changes in peak VO_2 as increase > 0.7 ml/min/kg, change of -1.7 to 0.6 ml/min/kg, and decrease of > 1.7 ml/min/kg. The patients who died, had an MCP within 6 months or VO_2 decreased >1.7 ml/min/kg are combined



Therefore, the results of functional testing are inconsistent with a marked clinical improvement with the CorCap.

XI. Structural measures

Remodeling of the left ventricle is detrimental to patients with heart failure and implies disease progression. Reversal of LV dilation alone does not constitute reversal of remodeling. Reversal of remodeling, as seen with beta blockers, includes reduction in LV mass in addition to changes in geometry. Ventricular reserve improvement would also be compelling to show reverse remodeling.

There are data missing in the structural endpoints analysis as follows: 30% in the MVR Treatment arm; 41% in the MVR Control arm; 42% in the no MVR Treatment arm; and 44% in the no MVR Control arm.

Acorn's Comment: This analysis calculates percent missing based on an analysis of paired data at 12 months. Thus, it depicts an inflated number because patients who did not contribute 12 month data because they were dead were counted as missing. In addition, per the study protocol, patients who had a VAD placement or a heart transplant were not required to contribute ECHO data after the VAD or transplant; the percent missing quoted counts this ECHO data as missing.

The first table below depicts the changes in LV volumes and dimensions both in diastole and systole, the EF, the LV mass and the sphericity index between the treatment and the control group. The subsequent table shows the same structural parameters divided by MVR vs. no MVR strata. All changes are shown at 12 months.

Table 13: Structural Changes

	Treatment (n=132)	Control (n=134)	p-value (ANOVA)
LVEDV	-32.7(n=97)	-17.2 (n=88)	0.21
LVESV	-25.9(n=97)	-8.2 (n=88)	0.10
LV EF	3.7	0.2	0.051
Sphericity	0.10	0.03	0.003
LV mass	-14.9 (n=50)	-13.6 (n=53)	0.86
LVEDD	-5.8 (n=114)	-3.6 (n=107)	0.002
LVESD	-4.8 (n=114)	-2.5 (n=105)	0.02

Acorn's Comment: Table 13 combines two types of analyses – treatment effect at 12 months using longitudinal regression analyses while presenting p-values from an ANOVA.

Table 14: Structural Changes by Strata

	MVR		noMVR	
	Treatment (n=91)	Control (n=102)	Treatment (n=57)	Control (n=50)
LVEDV	-39.9(n=64)	-25 (n=60)	-25.9 (n=33)	-12.4 (n=28)
LVESV	0.1(n=64)	0 (n=60)	-23.6 (n=33)	-6.0 (n=28)
LV EF	2.9 (n=64)	-1.2 (n=60)	4.4 (n=33)	1.5 (n=28)
Sphericity	0.12 (n=63)	0.03 (n=58)	0.08 (n=34)	0.04 (n=29)
LV mass	**-20.8(n=64)**	**-18.4 (n=60)**	**-8.2 (n=33)**	**-9.3 (n=28)**
LVEDD	-7.1 (n=62)	-4.8 (n=53)	-5.0 (n=27)	-2.5 (n=26)
LVESD	-5.4 (n=60)	-3.4 (n=53)	-5.1 (n=27)	-1.3 (n=26)

Therefore, the CorCap decreased LVEDV and LVESV in the Treatment arm when compared to the Control (the decrease was not statistically significant) with the largest difference in the noMVR group. Note that the largest reduction in LV mass index occurs in the MVR group and both Treatment and Control arms have similar reductions. Therefore, both decreases are clinically meaningful. There was a higher improvement in sphericity in the Treatment group compared to Control; the changes are not clinically meaningful. It is difficult to assess dimensions when using a mechanical constraint that could also change the shape of the ventricle. The changes in these clinical surrogates did not translate into changes of functional capacity or mortality. Although the Sponsor has presented data correlating cardiac structural changes to functional endpoints (see Sponsor panel pack), these data are difficult to interpret in light of the amount of missing data for CoreLab NYHA, Peak VO2 and QOL.

XII. Quality of Life: In an unblinded trial, the possibility of placebo effect exists when questionnaires are used for assessment of QOL.

- Quality of Life was assessed by the Minnesota Living with Heart Failure Instrument (MLWHF). Lower scores are interpreted as a better QOL. At 12 months there were 125 (84%) QOL assessments in the Treatment group and 119 (78%) in the Control group. Both groups improved their QOL scores. The Treatment group had a reduction at 12 months of 16.4 units vs 12.6 units in the Control group. Both groups, therefore, improved QOL. The difference between the 2 groups of 3.8 units is not clinically meaningful. The Table below depicts the changes by months in the MVR and NoMVR group.

Table 15: Quality of Life

	Treatment (n=57)		Control (n=50)	
NoMVR Stratum	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**Mean Change (95% CI)**
3 Months	49	-12.1 (-17.0, -7.2)	45	-6.3 (-11.4, -1.2)
6 Months	49	-8.9 (-14.2, -3.6)	40	-7.0 (-12.7, -1.2)
12 Months	45	-11.3 (-17.1, -5.5)	42	-6.4 (-12.4, -0.3)
18 Months	25	-12.3 (-21.0, -3.7)	23	-1.8 (-10.9, 7.2)
24 Months	21	-5.3 (-14.7, 4.1)	15	-1.1 (-12.0, 9.8)
	Treatment (n=91)		**Control (n=102)**	
MVR Stratum	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**Mean Change (95% CI)**
3 Months	84	-21.7 (-26.4, -16.9)	82	-16.1 (-20.8, -11.3)
6 Months	79	-21.7 (-26.7, -16.8)	82	-18.0 (-22.8, -13.1)
12 Months	80	-21.9 (-26.9, -16.9)	77	-18.3 (-23.3, -13.3)
18 Months	54	-20.0 (-25.2, -14.8)	50	-17.7 (-23.0, -12.3)
24 Months	35	-23.2 (-29.0, -17.4)	32	-18.3 (-24.3, -12.2)
	Treatment (n=148)		**Control (n=152)**	
All Patients	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**Mean Change (95% CI)**
3 Months	133	-16.6 (-20.1, -13.0)	127	-11.1 (-14.7, -7.5)
6 Months	128	-15.5 (-19.3, -11.8)	122	-12.6 (-16.4, -8.8)
12 Months	125	-16.4 (-20.2, -12.6)	119	-12.6 (-16.5, -8.7)
18 Months	79	-15.6 (-20.1, -11.2)	73	-11.1 (-15.6, -6.5)
24 Months	56	-15.5 (-20.6, -10.4)	47	-11.4 (-16.9, -5.9)

- An additional QOL instrument was used. The SF36 is a non-specific questionnaire with 2 domains: general health and physical function. A higher score is indicative of a better QOL. No specific value that equates to clinical significance for heart failure is widely accepted.

- The mean change in SF-36 at 12 months was 15.2 for the Treatment group (n=124) and 10.2 (n=92) for the Control group. The SF-36 is broken down in this table by MVR vs. NoMVR group with changes in baseline scores at several time points. The SF-36 shows small changes, mostly driven by the big difference in NoMVR patients (e.g. comparing no operation with operation, a big risk for placebo effect).

Table 16: Change (Post – Pre) in Physical Function Domain (SF-36) Score

	Treatment (n=57)		Control (n=50)	
NoMVR Stratum	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**Mean Change (95% CI)**
3 Months	49	9.7 (4.0, 15.5)	45	7.3 (1.3, 13.3)
6 Months	49	8.5 (2.9, 14.1)	40	1.4 (-4.6, 7.5)
12 Months	45	13.2 (6.9, 19.5)	42	4.2 (-2.4, 10.8)
18 Months	25	13.1 (5.0, 21.3)	24	4.7 (-3.7, 13.0)
24 Months	21	11.9 (1.8, 22.1)	15	4.8 (-6.7, 16.4)
	Treatment (n=91)		**Control (n=102)**	
MVR Stratum	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**Mean Change (95% CI)**
3 Months	83	18.5 (13.6, 23.3)	81	11.2 (6.4, 16.0)
6 Months	79	17.9 (12.8, 23.1)	82	11.6 (6.6, 16.6)
12 Months	79	17.9 (12.7, 23.1)	77	15.1 (9.9, 20.3)
18 Months	54	18.1 (12.5, 23.6)	50	15.6 (10.0, 21.3)
24 Months	35	16.6 (10.0, 23.2)	32	13.6 (6.8, 20.5)
	Treatment (n=148)		**Control (n=152)**	
All Patients	**# Patients**	**Mean Change (95% CI)**	**# Patients**	**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)

XIII. Brain Natriuretic Peptide BNP

The Sponsor has reported BNP as one of other secondary endpoints. The BNP relates to intraventricular volume and pressure. A rise in BNP is not desirable in an HF population, although values can vary with age, renal function, etc. Therapy that is directed at lowering filling pressures and volume as well as dimensions, should lower the BNP. Values over 100 are considered HF related.

There is a large amount of missing values for BNP. Values at baseline and 6 mos are shown below for patients with data at 6 mos.

Table 17: BNP Values

	Treatment		Control	
	#	Mean + SD	#	Mean + SD
Baseline	71	176.0 + 229.9	80	184.0 + 284.7
6 mos	106	238.3 + 307.6	104	176.7 + 211.4

Therefore, although missing data and having a wide SD, the Treatment group tended to have BNP increase whereas the Control group decreased slightly.

XIV. Adverse Events:

Constriction of the LV would impair filling and the use of the Frank Starling mechanism to improve cardiac output by increasing preload. A constricted ventricle would not be able to absorb increases in end-diastolic volume and would therefore rely on inotropic and chronotropic reserve to augment output**.** Such an early event could be captured in the amount of inotropes needed in the intensive care unit to respond to "hemodynamic compromise." As per Sponsor's submission, the following table relates any AE and any serious AE by treatment group.

Table 18: AE and Serious Adverse Events by Treatment Group

	Any Adverse Event					Any Serious Adverse Event				
	Treatment (n=148)		Control (n=152)			Treatment (n=148)		Control (n=152)		
	# Pts	% of 148	#Pts	% of 152	p-value	# Pts	% of 148	#Pts	% of 152	p-value
Hemodyanamic Compromise	90	60.8	75	49.3	0.05	90	60.8	74	48.7	0.14

Acorn's Comment: Data in Table 18 as of 15 April 2005. A single type of AE is presented, while data on total AEs and other types of AEs in the study is missing.

In the NoMVR stratum, there was no statistically significant difference in the percent of adverse events between the Treatment and Control groups. The Treatment group experienced more bleeding, infection, pulmonary compromise and renal compromise than the Control group, but none of these reached statistical significance.

The Treatment group (who received the CorCap) experienced significantly greater number of adverse events in the early 30 day postoperative period than the Control group ($p<0.001$): The Sponsor refers to this as the "up front cost" of the CorCap. These include: hemodynamic compromise ($p=0.007$), pulmonary compromise ($p=0.01$), and infection ($p=0.03$).

XV. Constrictive physiology

In light of the excessive amount of fibrosis and adhesions reported by surgeons when performing median sternotomy on patients with the CorCap, a possibility of constrictive physiology should be examined. The Sponsor has not reported any acute episodes of constriction in the early postoperative period using surveillance of symptoms and right heart monitoring. The Echo Core lab analyzed follow-up echos at 6 month intervals. Constriction is a diagnosis made by patient symptoms, physical signs and confirmation by echocardiography.

252 patients had echo data with 18 patients in the Treatment arm and 30 in the Control arm without follow-up echo. There were 43 patients (33%) in the Treatment group and 16 patients (13%) in the Control group with at least 1 echo with possible or suggestion of constriction ($p=0.0002$). The Agency has not reviewed the CRF's for patients with possible constriction and so an independent review of symptoms cannot be made. The Sponsor has provided a list of clinical notes and action taken for all patients with echo at any point suggestive of, or with, possible constriction. No patient had any action taken and there are no corresponding AE's for hemodynamic compromise associated. For the patients with at least one echo finding of possible constriction, there is no evidence that the outcomes were different than those patients with no echo findings of constriction. Such outcomes include death, death or serious AE, death or serious/moderate AE/ and inpatient hospitalization. Nonetheless, constriction in any open heart procedure can take years to become manifest. Since the followup time with repeat echoes is limited to 18 months post op, there are no data available to assess the presence or new onset of constriction beyond 18 months.

STATISTICAL

Study Description and Results

The trial had 2 arms: a total of 300 patients received appropriate medical therapy and, approximately half of the patients (n = 148) were randomized to also receive the CorCap. Randomization was blocked by site and stratified by whether or not a patient needed concomitant MVR surgery. Thus, there were four separate subgroups of patients: MVR + CorCap + meds (n = 91), MVR + meds (n = 102), CorCap + meds (n = 57), and meds only (n = 50). The sponsor

derived their sample size per CorCap/control group based on a power study, yielding about 80% power.

The primary effectiveness endpoint (evaluated after at least 1 year) was a composite of three elements: death (yes/no), major cardiac procedure (MCP) for worsening heart failure (yes/no) and change in NYHA class (improvement by 1 class [or more], no change, worsening). Each element of the composite was weighted equally. Patients were assigned a score of 1 if at 1 year they were alive, had not had a MCP and their NYHA class improved by at least one class. They were assigned a score of 2 if they were alive, had not received a MCP and their NYHA class was unchanged (compared to baseline). Patients were assigned a score of 3 if they were dead, or received a MCP, or if their NYHA class worsened by 1 or more classes. The total scores for each arm (CorCap vs. control) were compared using a proportional odds model, with covariates including whether MVR surgery was performed, time of enrollment (before or after July 4, 2002), size of site (small, medium, or large), diastolic blood pressure at baseline, gender, and peak VO_2 at baseline. The latter two covariates were determined to differ significantly (i.e., $p < 0.05$) at baseline between CorCap and control patients, with means that indicated a higher risk control group. However, there were 30 baseline variables measured; two variables might be expected to differ significantly at the 0.05 level by chance alone. (Two additional baseline covariates, diastolic blood pressure at baseline and years since HF diagnosis, did not differ significantly between groups, $p = 0.053$ and $p = 0.08$, but also had means that indicated a higher risk control group).

There were seven patients who withdrew or were lost to follow up prior to the 6-month visit. These patients were not included in the primary analysis. Thus, there were only 293 patients used in the primary analysis.

The fitted model showed a significant effect due to treatment arm, in that CorCap patients had 73% better odds of being in a better category (95% confidence interval on cumulative odds ratio: 1.07, 2.79). Percentages within the contingency table formed by endpoint category and treatment group showed that the CorCap group had a greater percentage of patients showing improvement on the composite, as well as a lower percentage of patients showing worsening (see Table 1; percentages are averaged over imputed data sets).

Table 1: Primary endpoint analysis (imputing missing data)

	Treatment (Average %) N = 147	**Control (Average %) N = 146**	**Odds Ratio T/C (95% CI)**	**p-value**
Improved	37.7	27.3	1.73 (1.07, 2.79)	0.02
Same	25.1	27.7		
Worsened	37.2	45.1		

The sponsor assessed the proportional odds assumption using the score test of Peterson and Harrell (1990). This test is implemented in PROC LOGISTIC and is a global test of proportional odds for all explanatory variables. The test gave a p-value of 0.93 for complete cases with both baseline and final NYHA, and a histogram of p-values that are mostly all above 0.05 for the imputed data sets.

The sponsor prospectively intended to examine a treatment effect within each MVR stratum, although the proposed sample size was not sufficient for 80% power within each stratum. Within the MVR stratum (193 patients), the estimated cumulative odds ratio was 1.51 (95% CI: 0.84, 2.72). Within the No MVR stratum (107 patients), the estimated cumulative odds ratio was 2.57 (95% CI: 1.09, 6.08). Similar percentage patterns in the contingency table occurred across strata. However, the magnitudes were larger in the No MVR stratum (see Table 2).

Table 2: Primary endpoint analysis within strata (imputing missing data)

No MVR Stratum N=107	**Treatment (Average %) N = 57**	**Control (Average %) N=50**	**Odds Ratio (95% CI)**	**p-value**
Improved	34.7	19.3	2.57 (1.09, 6.08)	0.032
Same	27.4	31.6		
Worsened	37.9	49.1		
MVR Stratum N = 193	**Treatment (Average %) N = 91**	**Control (Average %) N = 102**	**Odds Ratio (95% CI)**	**p-value**
Improved	39.6	31.3	1.51 (0.84, 2.72)	0.17
Same	23.6	25.7		
Worsened	36.8	43.0		

Many secondary measures show mean results that favor the CorCap group. However, most are not statistically significant (at the 0.05 level) under an appropriate multiplicity adjustment…

Acorn's Comment: The sponsor and the FDA prospectively defined a success criterion for the secondary endpoints which accounted for multiplicity in the form of the Hochberg. This criterion was met.

…Pages 46-54 of the Clinical tab in the Panel Pack, as well as the text below, discuss secondary measures.

REVIEW SUMMARY

1. Patient NYHA class was assessed by a site investigator or designee early in the trial. Near the middle of the trial, NYHA class was assessed by a blinded observer instead. Accordingly, the majority of patients had their NYHA class at entry assessed by the site and their final NYHA class assessed by a blinded observer. Site vs. blinded assessment of NYHA class is likely not the same. Thus, the endpoint of change in NYHA class could differ depending on whether the site investigator or blinded observer did the early assessment (and the sponsor has shown a low concordance between the two different NYHA measurements at baseline). The sponsor corrected for this by imputing blinded baseline NYHA data for those patients who only had the site assessment. The linear regression imputation model included covariates from the primary analysis model, as well as duration of heart failure, six-minute walk distance at baseline, LVEF at baseline, NYHA as measured by site investigator, and ischemic etiology. Multiple imputations were performed, assuming missingness at random (indeed, missingness was directly

dependent on time of enrollment). An ordinal imputation model (proportional odds model) was also used, with similar results. Unfortunately, more than half of the NYHA data had to be imputed, implying somewhat uncertain inference. An FDA analysis of the primary endpoint using only available data (i.e., cases without missing values on the composite) found that the CorCap group (n = 93; n = 56 with MVR surgery) had a greater frequency of improvement on the composite compared to control (n = 98; n = 63 with MVR surgery), as well as a lower frequency of worsening, when compared to the control. (See Table 3).

Table 3: Primary Endpoint analysis (using available cases only)

	Treatment (n=93)	**Control (n=98)**	**Odds Ratio T/C (95% CI)**	**p-value**
Improved	30.1%	18.4%	1.84 (0.94, 3.59)	0.07
Same	18.3%	22.5%		
Worsened	51.6%	59.2%		

2. Although the sponsor performed a test of the proportional odds assumption for the analysis model (that the treatment effect is the same when comparing "improved" vs not improved, and when comparing "improved or same" vs. "worsened"), the test they conducted is a global test of all explanatory variables, and is not always accurate (Harrell, 2001)…

Acorn's Comment: FDA withdrew this concern during its presentation at the Advisory Panel meeting on 22 June 2005.

…However, graphical assessment of proportional odds for each explanatory variable shows that the smoothed partial residual curves for the two cumulative logits are not parallel (in fact they cross) for MVR indicator and for the treatment group indicator. Furthermore, the observed cumulative odds ratios for available cases (excluding all cases missing a composite value) are given below in Table 4 across treatment group and across MVR stratum

Table 4a: Primary Endpoint Percentages (using available data)

	CorCap (n=93)	**Control (n=98)**	**Observed Cumulative Odds Ratios**
Improved	30.1%	18.4%	OR Y<= Improved = 1.92
Same	18.3%	22.5%	OR Y <= Same = 1.36
Worsened	51.6%	59.2%	

Table 4b: Primary Endpoint Percentages (using available data)

	MVR (n=119)	**NoMVR (n=72)**	**Observed Cumulative Odds Ratios**
Improved	26.1%	20.8%	OR Y<= Improved = 1.33
Same	17.6%	25.0%	OR Y <= Same = 0.92
Worsened	56.3%	54.2%	

Thus, the observed cumulative odds ratios from the available data differ depending on the outcome cutpoint.

However, FDA acknowledges that analyzing the primary endpoint only with available cases can give biased results, as data were not missing completely at random (i.e., irrespective of any observed or unobserved variables).

3. There are concerns regarding the multiple imputation amid the high proportion of missing data…

   Acorn's Comment: Independent imputation experts and FDA have confirmed the statistical robustness of the methodology.

   …When there is a higher proportion of missing data, there is greater sensitivity to missingness not at random and greater sensitivity to the imputation model. The sponsor performed imputation using two different imputation models, which gave similar results, but a comparison of Tables 1 and 3 show a decrease in percentage worsened in Table 3 for both treatment groups. This appears to reduce the cumulative odds ratio for improved versus not improved in the table with percentages averaged over imputations (Table 1). It is unclear whether it is possible that this difference could be an artifact of sensitivity to the imputation model, regardless of whether baseline NYHA is treated ordinally or continuously.

   Also, missingness was directly related to the time of enrollment of a patient, but it is unclear whether the missing baseline NYHA values could be systematically different from the known baseline NYHA values perhaps because of the way in which patients enrolled in the trial. A systematic difference could result in imputed data sets with biased baseline NYHA. The sponsor has attempted to address these concerns by including more covariates in the imputation model that could perhaps explain a difference between early and late enrollees. They have also performed multiple (100) imputations to reduce variance between imputed data sets. However, it is unclear whether the concerns are alleviated.

4. Although the primary endpoint analysis was only appropriately powered to detect a significant treatment effect in the composite, the elements of the composite endpoint were looked at individually in order to determine which components contribute more to the overall composite significance (this analysis was prespecified in the protocol). Note that because the familywise error rate was not controlled a priori for these component analyses, any p-values cannot be interpreted in the same way as for the primary endpoint analysis. That is, the significance level with which to compare the p-values is unknown due to multiplicity issues.

   - There was no statistically significant treatment difference (CorCap vs. controls) in mortality. Kaplan-Meier survival curves appear on pages 26 and 27 of the Clinical Summary tab in the Panel Pack, and a log-rank test of the difference in curves yielded a p-value of 0.85 (an updated version to account for deaths up to April 15, 2005 gives

a p-value of 0.59). Up to the CCD, there were 25 deaths in each treatment group (see Table 5a below). Most deaths were adjudicated by the CERC as due to a cardiovascular cause.

Table 5a: Cumulative Number Deaths by Time

	Treatment N = 148	**Control N = 152**
30 Days	7 (4.7%)	1 (0.7%)
12 months	19 (12.8%)	21 (13.8%)
24 months	22 (14.9%)	24 (15.8%)
Up to CCD	25 (16.9%)	25 (16.4%)
As of 4/2005	29 (19.6%)	33 (21.7%)

Because 3 of the CorCap patients and 5 of the Control patients who died had experienced an MCP prior to death, these patients did not contribute deaths to the composite, but instead contributed MCPs. Thus, the cumulative number of deaths contributed to the composite is given below in Table 5b.

Table 5b: Cumulative Number Deaths by Time

	Treatment N=148	**Control N=152**
30 Days	6 (4.1%)	1 (0.7%)
12 months	17 (11.5%)	16 (10.5%)
24 months	19 (12.8%)	19 (12.5%)
Up to CCD	22 (14.9%)	20 (13.2%)

- A proportional odds model that used the same categories as for the primary composite, but only using change in NYHA class, eliminating any patients who died or had an MCP, gave an estimated odds ratio of 1.64 (95% CI: 0.87, 3.08), in favor of CorCap (see Table 7 and accompanying text). Patients who died did not have a measured final NYHA class at the CCD.

- The third component was number of MCPs. There were fewer patients in the CorCap group who received a MCP (see Table 6).

Table 6: % of patients needing *any* MCP

	CorCap	**Control**
No MVR	5/57 = 8.8%	12/50=24%
MVR	14/91=15.4%	21/102=20.6%
Total	19/148 = 12.8%	33/152 = 22%

(Pages 36, 65, and 74 of the Clinical Summary tab in the Panel Pack contain a breakdown of the types of MCPs by treatment group; two CorCap patients had multiple procedures, whereas 11 control patients had multiple procedures). The sponsor reported that a

Cochran-Mantel-Haenzel test comparing the two treatment groups (and controlling for site size, MVR stratum, and length of follow-up) found that the control had more MCPs ($p = 0.014$). Although the sponsor did not report an estimated odds ratio or confidence interval in the submission, FDA attempted to reproduce the analysis, and calculated an odds ratio of 2.22 with 95% CI of (1.16, 4.20).

In addition, the sponsor analyzed time to first MCP. Kaplan-Meier curves appear on page 35 of the Clinical Summary tab in the Panel Pack. A Cox proportional hazards regression on the time to first MCP showed a hazard ratio in favor of CorCap (0.46, $p = 0.01$). For time zero, the sponsor used time of surgery for the CorCap group, and time of randomization for the control group. However, an FDA analysis found that using time of randomization for all patients makes little difference in the estimated survival curves and in the Cox model results.

It appears that the number of patients who received MCP for worsening heart failure contributes a great deal to the statistical significance of the composite results. FDA clinicians believe that some patients who received MCP should not be automatically counted as "worsened" on the composite endpoint because they received MCP for reasons other than worsening heart failure (e.g., because of problems with previous MVR surgery). For five patients (4 control, 1 CorCap) there is a disagreement between FDA clinicians and the sponsor's CERC. However, if these 5 patients are eliminated from the analysis, then results do not change with respect to statistical significance, according to FDA's analysis (95% CI on odds ratio (1.02, 2.68), $p = 0.04$). It is unclear if these five patients were *reclassified* using either death or their NYHA change, whether there would be a change in statistical conclusion. We know that one control patient died sometime after their MCP, but before the CCD. For the remaining four patients, a worst-case analysis done by FDA that assigns an "improved" status to the 3 controls and a "worsened" to the CorCap yields an estimated odds ratio of 1.56 with 95% CI (0.972, 2.51). Thus, even under an extreme assumption regarding the actual status of these four patients, any disagreement between FDA and the sponsor's CERC does not appear to unduly affect the outcome of the primary analysis.

In addition to disagreeing with some of the reasons for receiving MCP, FDA is concerned that, because some CorCap patients were seen to be difficult cases for re-operation, physicians might have been reluctant (biased) to refer CorCap patients for MCP, or delay referring CorCap patients for MCP. This might have affected the relative number of patients with MCP in the CorCap and control groups, thus altering the outcome of the statistical analyses. There is no way to determine definitively, using the data, whether such a bias occurred. However, there are several points to make:

a. When change in NYHA is considered alone, eliminating those patients who either died or had an MCP that already counted toward the primary endpoint (94 patients), there is an increase in percentage improved on NYHA (using the imputed data) for the CorCap vs. control groups (see Table 7).

Table 7: Change in Core Lab NYHA (removing MCP and death)

All Patients	Treatment (Average %) N = 107	Control (Average %) N = 99	Odds Ratio T/C (95% CI)	p-value
Improved	52.3	42.8	1.64 (0.87, 3.08)	**0.12**
Same	34.8	43.4		
Worsened	13.0	13.8		

Generally speaking, a reduction in MCP for the CorCap patients vs control patients cannot account for an increase in "improved" percentage on NYHA unless many patients who needed an MCP were also improved on NYHA. In this case, a treatment bias would keep CorCap patients who needed an MCP in the improved category, instead of moving them to "worsened" and thus create a difference in improved as well as worsened categories across treatment groups.

Because the greatest observed difference in MCPs across treatment groups lies in the most serious procedures (LVAD or transplant, see Table 8), if there had been a treatment bias and CorCap patients who needed these MCPs for worsening heart failure were not getting them, then these patients might be assumed to have worsened on NYHA or possibly to have died during the trial. Thus, the percentages in Table 7, as well the lack of observed mortality difference between groups do not appear to support the notion that a treatment bias is completely responsible for the statistically significant results.

Table 8: % of patients needing LVAD or transplant

	CorCap	Control
No MVR	1/57 = 2%	7/50 = 14%
MVR	8/91 = 8.8%	13/102 = 12.7%
Total	9/148 = 6.1%	20/152 = 13.1%

However, the above reasoning assumes that patients were getting MCPs due to worsening heart failure (FDA challenged the adjucations for 5 patients, as discussed in the third bullet point under 2 above). Also, the estimated odds ratio in Table 7 is not significantly different from 1.0, by any conventional significance level, indicating that the probability of the percentages in Table 7 occurring when there really is no treatment effect is unacceptably high.

Nonetheless, if in fact there is a treatment bias in MCP, one way to reassess the primary endpoint could be to disregard MCP and only look at death or each patient's NYHA class at the common closing date to determine their category on the composite endpoint. However, this reassessment cannot be done because, according to the sponsor, the NYHA class at the common closing date was not recorded for those who were classified as getting an MCP for worsening heart failure. The sponsor assumes that patients who got an MCP for worsening heart failure would be classified as IV on the NYHA scale at the CCD. If we use that classification, then the primary analysis result remains significant (p = 0.044), by an FDA analysis.

However, the assumption of class IV on NYHA might not be appropriate. Indeed, a tabulation done by FDA found that 13 of 22 patients (5 CorCap; 8 control) who are listed in the database as having had an MCP for worsening heart failure after 12 months follow-up, and also as having available a result on a variable labeled as "follow-up core lab NYHA classification month 12 or later", are classified as NYHA Class II or III. This tabulation appears to indicate that a patient might be considered better than Class IV on NYHA, but also have an MCP. Furthermore, it is possible that a patient who had an MCP also improved on NYHA class assessment from baseline. Of the 13 patients mentioned above for whom baseline site NYHA was recorded, 5 improved (2 CorCap) on NYHA from their baseline site assessment.

Finally, in an unblinded trial, the possibility that placebo effect contributes to an observed treatment effect, partially measured by subjective assessments such as NYHA or quality of life, is relatively greater than that in a double blinded trial.

b. Statistical results from major secondary performance measures are mixed with respect to showing a possible CorCap effect. (Significance is determined based on the Hochberg procedure. P-values are adjusted for multiplicity).

- Change in site-assessed, unblinded, NYHA (in categories improved, same, worsened) does not show a significant treatment effect. An FDA analysis that used the last recorded NYHA class after 12 months as the final NYHA class obtained an estimated odds ratio of 0.88, which was not found to be significantly different from 1 ($p = 0.98$). Since referrals for MCPs were done by the site physicians, one might expect that those patients who were referred would also score worse on site NYHA assessment, if referral for MCP implied worsening heart failure. This notion has not been fully explored by FDA; however, the above estimated odds ratio favors the control group, who received relatively more MCPs, and thus should be relatively worse off on site-assessed NYHA.

- Average reduction in LVEDV over time was significantly greater in the CorCap group (mean difference over time = -17.9 ml, adjusted $p = 0.032$)

- Change in mean LVEF over time was not significantly different across groups (mean difference over time = 0.83%, adjusted $p = 0.98$).

- Change in mean MLHF over time was lower for the CorCap group (mean difference over time = -4.47, adjusted $p = 0.12$).

- Objective secondary measures of functional performance (such as peak VO2 and 6-minute walk distance) had a large amount of data missing not at random (e.g., from sicker patients). Thus, the results from analyzing these variables are not easily interpretable. Also, familywise error rate was not controlled in assigning a significance level for these endpoints.

5. The sponsor found that the estimated cumulative odds ratio on the composite endpoint within the NoMVR stratum (n = 107) is higher than the estimated cumulative odds ratio in the MVR stratum (n = 193) (see Table 2), although both odds ratio are in the same direction, favoring CorCap. A test for an interaction between MVR stratum and treatment group that controlled for the same covariates used in the primary analysis gave a p-value of 0.44. According to this interaction test, significant results found within MVR strata might have an unacceptably high probability of having occurred by chance.

   Acorn's Comment: Acorn disagrees. This interaction test does not support the conclusion that significant results found within MVR strata might have an unacceptably high probability of having occurred by chance.

   A much larger reduction in MCPs for the CorCap was found in the No MVR stratum, a stratum where the control group received no operation (see Table 5). The calculated odds ratios for the rows of Table 6 are 3.28 in the No MVR stratum (95% CI: 0.96, 12.79) and 1.43 in the MVR stratum (95% CI: 0.638, 3.56). A test for homogeneity of odds ratio across strata was not found to be significant (p = 0.32). For LVAD and transplant (see Table 8), the odds ratios showed a greater difference between strata: 9.12 in the No MVR stratum (95% CI: 1.09, 418.0), and 1.52 in the MVR stratum (0.548, 4.44). A test for homogeneity of odds ratios across strata was not found to be significant (p = 0.18).

   There was less of a difference in cumulative odds ratios on change in NYHA alone (see Table 9), and almost no differences in the comparison of mortality survival curves across groups.

Table 9: Change in Core Lab NYHA (removing MCP and death)

No MVR Stratum	**CorCap (Average %)**	**Control (Average %)**	**Odds Ratio**
Improved	47.0	31.5	2.37 (0.72, 7.79)
Same	37.2	51.6	
Worsened	15.7	16.9	
MVR Stratum	**CorCap (Average %)**	**Control (Average %)**	**Odds Ratio**
Improved	55.7	48.2	1.45 (0.66, 3.20)
Same	33.2	39.5	
Worsened	11.2	12.3	

Although comparisons within MVR strata were secondary analyses, and therefore, are subject to a stricter significance level, it should be noted that the sample size within the MVR stratum is almost double that in the NoMVR stratum, and the relative percentages of CorCap vs. control patients are approximately balanced within each stratum (see Point 1 above). Furthermore, an examination of the primary endpoint within each stratum was prospectively specified by the sponsor, even though the sample size did not provide adequate power to detect a potential effect. Thus, an observed difference could be worthwhile to examine further.

CONCLUSIONS

- The sponsor has met the primary endpoint. The only component contribution to the composite that shows statistical significance (at the 0.05 level) is additional major cardiac procedures. However, statistically, it is difficult to determine whether a referral bias by physicians is responsible for the significance seen in the number and rate of additional major cardiac procedures, or whether the result is significant because the CorCap reduces the likelihood of having a cardiac procedure due to worsening heart failure. In the NYHA contribution to the primary endpoint, there is an observed improvement for the CorCap group, which does not reach statistical significance (although it excludes patients who died and who had MCP). A referral bias for MCP could exist simultaneously with an observed improvement in NYHA if patients who got MCP did not necessarily always worsen on NYHA, but could have improved. (FDA has identified patients for whom this is the case, as discussed in Subsection a of Section 2 above).

- The primary endpoint analysis involved imputation of a large amount of missing baseline NYHA data. Imputation of such a large amount of data could result in uncertain inference.

  Acorn's Comment: The sponsor has demonstrated the robustness of the imputation results.

- Many secondary measures of mean performance favor CorCap group. However, most are not significant according to a multiplicity adjustment. Furthermore, objective measures such as peak VO_2 and 6-minute walk did not show statistically significant improvements in the CorCap group, but also contain too much data missing not at random. This creates problems in interpretation.

- An observed treatment difference seen between the NoMVR and MVR strata could be worth examining further.

POST-MARKET FOLLOW-UP

The Condition of Approval (CoA) study proposed by the sponsor is postmarket surveillance to examine the performance of up to 348 patients with the CorCap CSD for 5 years. As in the IDE clinical trial, principle variables include NYHA classification, mortality, adverse events, and echo measurements. The proposed surveillance has the following components:

A. Extended Follow-up Phase
   1. 148 patients fitted with the CorCap CSD from the clinical trial
   2. Data collection differs from the clinical trial in that the assessment of NYHA, 6-minute walk test, CPX testing, blood tests, BNP ECG, MLHF, and SF-36 will not be collected.

B. Continued Access Protocol (CAP)
   1. 100 new patients enrolled at sites that participated in the IDE, with similar inclusion criteria
   2. CAP differs from the clinical trial in the pre-enrollment phase in that:

        a. lab tests indicative of surgical readiness will be conducted at the discretion of the surgeon; and,
        b. no biventricular valve exclusion criteria.
    3. CAP differs from the clinical trial in the follow-up phase in that:
        a. no blinded assessment of items in A2,
        b. no 3-month follow-up (starts at 6 months); and,
        c. echos will be analyzed by site cardiologist rather than by core lab.

C. Postmarket Surveillance Study
    1. 100 new patients enrolled at 10 U.S. sites that did not participate in the IDE, but with similar inclusion criteria
    2. Identical to CAP in all other characteristics.

Data from the three surveillance components are to be pooled and submitted to FDA in an annual report.