

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

**FDA REVIEW MEMORANDUM – 1 FEBRUARY 2006  
CORRECTIONS AND CLARIFICATIONS\***

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**MEMORANDUM**

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**TO:** P040049/A005 & A006  
**FROM:** Matt Hillebrenner  
**SUBJECT:** Acorn CorCap Cardiac Support Device (CSD)  
**CONTACT:** Acorn Cardiovascular, Inc.  
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**DATE:** February 1, 2006  
**CC:** Ann Ferriter

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This memo will provide a synopsis of FDA's entire post-panel review of the file and specifically cover FDA's review of Acorn's most recent submissions, P040049/A005 & A006.

The Acorn CorCap CSD was reviewed at a Circulatory Systems Advisory Panel Meeting on June 22, 2005. Up to and including this meeting, Dr. Michael Berman was the lead reviewer for this file. Dr. Berman has since moved to the Office of Science and Engineering Laboratories. He remains involved in the ongoing review of the file as a consultant. Matt Hillebrenner has assumed lead reviewer responsibilities. In summary, the advisory panel voted by a count of 9-4 in favor of a Not Approvable decision for the CorCap device, citing both safety and effectiveness concerns. After the panel meeting, Acorn requested a follow-up discussion with FDA to obtain feedback on how they should proceed. Prior to a face-to-face meeting held on July 19, 2005, Acorn submitted to FDA a proposal for a retrospective reanalysis of the current data set. The goal of this analysis was specifically to exclude patients who were at high risk for peri-operative mortality, one of the main issues raised at the panel meeting. This proposal was reviewed by all members of the FDA review team prior to the meeting with the company. Dr. Clyde

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

Yancy, one of the panel's primary reviewers, continues to contribute to the review team as well. During the meeting with the sponsor, FDA raised several concerns related to the proposed reanalysis and offered additional suggestions for ways they could bolster their argument. Another meeting was held with the sponsor on July 29, 2005. This meeting was requested by the sponsor to discuss the regulatory timelines and strategy moving forward. At this meeting, FDA informed Acorn that we would be sending a post-panel letter to summarize the review of the panel and update FDA's position on the file.

In concurrence with the panel's recommendation, we believed that the sponsor had not established a reasonable assurance of safety and efficacy for the CorCap device. FDA still had outstanding safety concerns such as peri-operative mortality, safety of re-operation due to adhesions, and the long-term risk of constrictive pericarditis. There remained a large amount of missing data for the primary effectiveness endpoint and no statistical significance in a number of secondary endpoints, which left FDA with no specific patient population in which the device was shown to be effective.

On August 12, 2005, FDA issued a Not Approvable letter to the company. Due to the shortcomings described above, FDA chose to provide general deficiencies in the Not Approvable letter as opposed to listing out each and every remaining issue...

**Acorn's Comment: Acorn believes that this lack of specificity impeded the sponsor's ability to address FDA's concerns. FDA is required by the regulations to provide the specific grounds for denial of a PMA. 21 CFR 814.44 (f) requires that where a Not Approvable decision is made, the Agency:**

**"...describe the deficiencies in the application, including each applicable ground for denial under section 515(d)(2) (A)-(E) of the act, and, where practical, will identify measures required to place the PMA in approvable form."**

...In addition, we listed three potential options for the sponsor to consider in their attempt to mitigate FDA's concerns. These options included a retrospective reanalysis of the current data sets (US and OUS) to establish a patient population in which the device is safe and effective. While FDA hesitated to completely rule out the option of a reanalysis of the current available data, we felt that the existing problems with the data would prevent the sponsor and FDA from reaching the goal of approval. In the letter sent to the company, FDA expressed the fact that we had concerns regarding the use of retrospective *post hoc* analyses alone. Therefore, we thought a better suggestion would be for the sponsor to perform a reanalysis of the current data to identify a target patient population in which the device appears to be safe and effective. Then the sponsor could conduct an additional (smaller) clinical trial in this targeted patient population, potentially using historical controls from the first study.

Despite FDA's acknowledged preference for the collection of additional prospective clinical data, the company has maintained that they do not have sufficient monetary funds to conduct a follow-up clinical trial and that reanalysis is their only option...

**Acorn's Comment: Acorn did not decline to conduct a second premarket study due to lack of funds. Acorn maintains that another clinical trial is not needed because the safety and effectiveness of the CorCap CSD were demonstrated in the original 300 patient pivotal trial. In addition, the small confirmatory trial described by FDA would not produce scientifically valid or robust data, and would delay the availability of the CorCap CSD for an unacceptable length of time.**

...As a result, Acorn then submitted PMA Amendments 5 and 6, containing the results of their *focused cohort analysis*.

These submissions were reviewed by several members of the FDA review team. Documentation of their reviews can be found in the attachments as indicated below. Also, a face-to-face meeting with the company was held on January 11, 2006. Acorn presented their focused cohort analysis at this meeting; in addition, they asked several of the investigators involved in their trial to give testimony related to their experiences with the CorCap. A summary of FDA's review and the meeting with the company are included here.

Dr. Clyde Yancy (Clinical) – Attachment 1  
Dr. Laura Thompson (Statistical) – Attachment 2  
Dr. Ileana Pina (Clinical) – Attachment 3  
Dr. Julie Swain (Clinical) – Attachment 4  
Meeting Minutes (January 11, 2006) – Attachment 5  
Acorn Presentation Slides (January 11, 2006) – Attachment 6  
Updated Mortality Analysis – Attachment 7

In order to identify the focused cohort, the company used a cumulative trends analysis (authored by Califf and DeMets) to comprehensively screen relevant baseline characteristics and to assess which ones identified the patients who had the largest and most consistent treatment vs. control difference (i.e., the patients who benefit the most from surgery). In summary, 19 variables were investigated for their effect on up to 8 key response variables or clinical outcomes in an effort to determine which baseline variable would be the best predictor of treatment benefit. The results of this analysis indicated that Left Ventricular End Diastolic Dimension indexed to body surface (LVEDDi) was the best predictor of patient outcomes in the trial. After examining the relationship between LVEDDi and several clinical outcomes, the sponsor determined that patients in the range of  $30 \text{ mm/m}^2 < \text{LVEDDi} < 40 \text{ mm/m}^2$  benefited the most from surgery. The focused cohort excludes patients with the smallest hearts, who are typically the healthiest patients and the least likely to benefit from treatment as compared to control. Also, the focused cohort excludes patients with the largest hearts, typically the sickest of the patients and those who are at higher risk for experiencing peri-operative mortality. While this does seem like a worthy goal, the company has used the same data set to both identify the predictor and test its validity, which raises questions about the integrity of the analysis. In addition, the sponsor looked at 19 variables to find the best possible predictor without

adjusting for multiplicity. Laura Thompson's review memo (Attachment 2) covers these issues in much greater detail.

Acorn claims that they were able to clinically validate the results of their focused cohort analysis through a comprehensive review of the proposal by several heart failure experts. FDA believes that this review was done after the fact and these experts may have been led into the conclusion that the specific LVEDDi range was meaningful since the analysis had already been conducted. Furthermore, some of the clinicians representing the company at the January 11<sup>th</sup> meeting clearly indicated that they did not foresee LVEDDi as being the best predictor for patient outcomes.

**Acorn's Comment: Meeting minutes agreed upon by Acorn and FDA indicate that physicians commented that they did in fact expect LVEDDi to be a predictor for patient outcomes.**

While acute mortality may have been mitigated using this analysis, this reviewer remains unconvinced that the sponsor has actually identified a patient population in which we can be reasonably sure the device is both safe and effective. For example, the graphs presented on page 14 of 73 (P040049/A005, Attachment A) do not demonstrate consistent benefit in the patient range of  $30 \text{ mm/m}^2 < \text{LVEDDi} < 40 \text{ mm/m}^2$  for outcomes involving death, HF hospitalization, transplant, or LVAD placement. Also, Dr. Thompson had requested an updated mortality analysis on the entire 300-patient cohort during FDA's review of this submission. The company submitted this updated analysis (including data collected through December 30, 2005) via email and a hard copy is included in Attachment 6.

Acorn attempted to address other specific concerns mentioned in the Not Approvable letter as well. For example, they asked several of their cardiovascular surgeons to speak to FDA regarding their experience performing re-operations on CorCap patients. At the panel meeting in June, specific mention was made of some of the operative reports describing dense adhesions associated with the CorCap and the difficulty of performing re-operations in these patients. Drs. Patrick McCarthy and Michael Acker both spoke about their clinical experience at the January 11<sup>th</sup> meeting. While these testimonials were interesting, the fact remains that these re-op procedures may be more complicated in patients with a CorCap, leading to a potential bias associated with one of the components of the primary composite endpoint – the need for a major cardiac procedure to treat worsening heart failure. This also happened to be the only component of the primary composite endpoint that met statistical significance in favor of the treatment group. The mortality analysis did favor the treatment group, but was not statistically significant.

**Acorn's Comment: FDA's review memo, dated 5/23/05, suggests that major cardiac procedure results were not explainable by treatment bias, as excerpted below.**

**Excerpt from FDA review memo, page 25**

***Because the greatest observed difference in MCPs across treatment groups lies in the most serious procedures (LVAD or transplant, see***

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**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 [Table 7 represents change in NYHA classification, which favors CorCap], 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.**

The analysis of the third component, NYHA status, was complicated by a large amount of missing data. This problem occurred because the sponsor began their trial using unblinded site-assessed NYHA status for patients' baseline measurements and switched to core lab-assessed NYHA status mid-way through the trial. Comparisons of the core lab- and site-assessed NYHA status in subjects who had both measurements at baseline indicated a low level of agreement between the two measures. Therefore, the sponsor was forced to impute approximately 60% of the data for this component of the primary endpoint. Without imputation, the results favored the treatment group but were not statistically significant.

Further clouding the interpretation of the study results was the fact that some patients needed concomitant mitral valve repair/replacement surgery and others did not. As a result, it was difficult to determine the effect of the CorCap device alone in patients who also had MVR surgery. In patients who did not need MVR surgery, the benefits of the device were easier to understand; however, the inherent risk of the device implantation was increased since these patients were not already having surgery performed.

Another concern mentioned in the Not Approvable letter is the lack of statistical significance in any secondary endpoints. This statement may have been better phrased as any *clinically meaningful* secondary endpoints...

**Acorn's Comment: FDA never clarified the specific meaning of this deficiency to Acorn in previous FDA interactions and correspondence, including in the not approvable letter for the CorCap PMA. Therefore, Acorn did not have an opportunity to fully address this concern in the amended PMA. Acorn maintains that the significant differences in secondary endpoints are clinically meaningful.**

...The sponsor maintains that their original trial and the focused cohort analysis demonstrated significance with regard to several secondary endpoints. This assertion does not take into account multiplicity adjustment for the focused cohort analysis.

**Acorn's Comment: The sponsor demonstrated statistical significance of secondary endpoints in the original 300 patient trial. The focused cohort analysis was not required to demonstrate success in secondary endpoints; it is intended to augment the original results.**

Regardless, the specific endpoints that favored the CorCap treatment were LVEDD, LVESD, LVEDV, LVESV, LVEF, Sphericity, and LV Mass. This list is dominated by cardiac dimension measurements. Given the constrictive nature of the device, it comes as no surprise that it would be able to reduce the dimensions of the heart. In order for these changes to be interpreted as clinically meaningful, there must be some improvement in functional outcomes tied to this response. Unfortunately, the sponsor was unable to demonstrate a treatment effect on cardiopulmonary exercise testing and other clinical outcomes.

**Acorn's Comment: These statements omit the favorable results in the secondary endpoints that support the claim of functional improvements in CorCap CSD patients. A summary of the secondary endpoint results in the original 300 patient trial, which demonstrated favorable results in functional endpoints including SF-36 GHD, SF-36 PFD, and MLHF, is provided below.**

Secondary Endpoints	Treatment Difference (T-C)	p-value
Hochberg Analysis of Major Secondary Endpoints	N/A	0.032
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	-5.9 g/m <sup>2</sup>	0.15
LVEDD	-1.8 mm	0.02
LVESD	-1.2 mm	0.21
Functional Endpoints	Treatment Difference (T-C)	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	Un-interpretable	
Cardiopulmonary Exercise Testing	Un-interpretable	
Other Endpoints	Treatment Difference (T-C)	p-value (odds ratio)
BNP	77.33 pg/ml	0.014
Re-Hospitalizations	1.0	0.44
Mortality or Re-Hospitalizations	N/A	0.88 (1.02)
Major Cardiac Procedures	N/A	0.01 (0.46)
Global Test	N/A	0.71

FDA also listed the possibility of long-term pericardial constriction as a concern associated with the CorCap device. The sponsor has proposed to study this effect in a robust 500-patient post-market study. Given the nature of this condition, it may make sense to monitor CorCap patients long-term in order to evaluate it. FDA would probably be willing to examine this in a post-market setting as well.

FDA believes that the focused cohort analysis provides a clear step in the right direction for the CorCap technology. However, we also believe that this hypothesis of a target patient population needs to be tested prospectively in order to be clinically validated. The sponsor has proposed to conduct this study in a post-approval setting. However, FDA believes that this data needs to be collected pre-approval in order to provide a reasonable assurance of safety and effectiveness. We are not asking the sponsor to duplicate the effort put forth in their original trial; we expect that this would be a one-arm trial using historical controls from the original study. We plan to include language in the Not Approvable letter that is sent to the company summarizing the views outlined in this paragraph.

**Recommendation:**  
 We recommend that this PMA be found Not Approvable.

Reviewed by:	<u>M. G. Hillebrunner</u> Medical Director, Lead Reviewer	<u>2/2/2006</u> Date
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