

To: **Medical Devices Dispute Resolution Panel**

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As members of the Steering Committee for the Acorn Randomized Trial, we are writing to express three important messages:

1. Patients with heart failure experience significant limitations in their quality of life, have severely limited life expectancies and are in great need of additional treatment options.
2. The Acorn CorCap CSD is supported by data from a comprehensive pre-clinical database that has demonstrated the proof of concept and an extensive clinical experience that has demonstrated patient benefit.
3. We strongly feel that these cumulative data meet the expected and defined standards for approval and that the Focused Cohort analysis provides a well-defined and narrow patient population that will derive benefit from this new therapy.

Based on our extensive experience in treating patients with heart failure, and in conducting clinical trials evaluating new therapies, we believe that we are qualified to describe the expected benefits of the CorCap™ Cardiac Support Device (CSD). Further, two of us (H. Sabbah and M. Acker) have specifically studied the effects of the CorCap CSD in accepted animal models of heart failure. We have been involved with and provided guidance in every aspect of the trial, including but not limited to, trial design, patient recruitment, study conduct at our respective sites, data analysis, scientific presentations and numerous meetings with the Division of Cardiovascular Devices (DCD). Thus, we are confident that, as a group, we have the appropriate qualifications from which to provide commentary on the safety and efficacy of the CorCap CSD.

#### Clinical Problem of Heart Failure

The impact of heart failure on individual patients and the American health care system is enormous. There are over 5 million patients living with heart failure in the United States, and heart failure is the most common diagnosis-related group for hospitalizations in the

Medicare population. The mortality rate for patients with advanced heart failure is extremely high, with a survival rate of only 50% at 5 years.

More importantly, our patients suffer from a significant deterioration in quality of life because of symptoms that are progressive despite medical therapy. Further, device and surgical options for heart failure are limited. For example, heart transplantation is limited to 2000 patients per year because of donor shortages. Simply put, there are limited alternatives for the treatment of our patients with heart failure, and the medical community is very much in need of new therapies that target different aspects of heart failure.

### Scientific Database

The CorCap CSD has been extensively studied and described in the peer-reviewed literature (58 manuscripts, 78 abstracts). This large body of clinical and technical data offers the CorCap PMA significant additional support, and is indicative of the high level of interest which the medical community associates with this technology.

Proof of concept studies were completed in 3 different animal models of heart failure, including coronary microembolism in the dog, rapid ventricular pacing in sheep and acute coronary ligation in sheep. The findings in all 3 models were remarkably consistent – a simple synthetic “wrap” without any actively moving parts could relieve wall stress and allow the heart to “repair” itself over time, as evidenced by a decrease in heart size, a return to a more elliptical shape and an increase in pumping function.

The sponsor has also conducted a number of important laboratory studies evaluating the effects on myocardial cell structure and function, biochemistry and molecular gene products. It is important to make a clear distinction between the CorCap CSD and a corset – there is convincing proof that individual myocardial cells from hearts that have the CorCap CSD device are smaller and function better than those in control hearts. Further, there are important improvements in oxygen diffusion, calcium handling and expression of fetal genes - all of which are critical factors in the pathophysiology of heart failure. Thus, in contrast to other new device interventions, the clinical and scientific community has a sound appreciation for how and why this device benefits heart failure patients.

Based on the compelling pre-clinical data, we approached the CorCap pivotal trial enthusiastically and were eager to evaluate if patients would derive the same level of benefit as predicted by animal studies. It is well recognized that designing controlled clinical trials evaluating these types of devices is a challenge given the lack of predicate devices and the ethical concerns that would arise if patients were subjected to sham open chest surgery. Thus, we appreciated the many teleconferences and meetings with DCD to collaboratively design a meaningful clinical trial. Ultimately, we conducted the largest trial ever completed for a device requiring open heart surgery; enrolling 300 patients in a prospective, randomized and controlled study including 29 centers. It is worth noting that we the investigators and the sponsor agreed to three demanding design features suggested by the DCD including increasing enrollment from 170 to 300 patients, extending follow up from 6 months to a minimum of 12 months, and further modifying the primary endpoint to

one which met the FDA criterion for “clinically meaningful” changes. These outcomes reflect the collaborative nature of the discussions that ultimately enhanced the scientific quality of the study. In fact, at the annual meeting of the Association of Thoracic Surgeons (April 10-13, 2005), Dr. Craig Miller of Stanford University described this trial as the “gold standard” for surgical trials.

We had follow-up on 299 of 300 patients. And notably, the protocol-specified<sup>1</sup> success criteria for the primary endpoint (p=0.024) and the secondary endpoints (p=0.03) were met. Patients who were treated with a CorCap Cardiac Support Device required fewer additional therapies (such as LVADs and transplants) and had immediate and sustained improvements in quality of life (as evidenced by significant increases in two separate quality of life measures). Further, patients treated with a CorCap CSD demonstrated important improvements in ventricular size and shape, as demonstrated by the significant decrease in LV volume and improvement in sphericity index. All of these changes are clinically meaningful for this population of patients who suffer persistent or progressive symptoms of heart failure despite optimal medical therapy.

#### Focused Cohort Analysis

One of the underlying challenges that confound investigators studying any new therapy is to identify patients who are most likely to have a positive outcome. This is especially true for a surgical intervention. We are pleased with the results of the Focused Cohort analysis. This analysis was originally presented to DCD to mitigate some of the concerns about relative risk and benefit. However, this analysis offers us a way to subdivide the large population of patients with heart failure into a much more narrow but very easy to understand and well defined subpopulation. The data on patient outcomes in this “focused cohort” is compelling and will increase the confidence of the cardiologist and surgeon that their patient will have a very good outcome.

#### Summary

In summary, we find the CorCap CSD to be an important new treatment for patients in great need of additional therapies and who currently have very limited options. The fundamental mechanism of action and proof of concept for this product have been extremely well validated and extensively published. The results of a large 300 patient prospective, randomized, controlled study confirm the safety and efficacy of the device. We strongly feel that the cumulative scientific database on this device has met the standard for approval and that this important device should be made available to physicians treating patients with heart failure.

We look forward to discussing these important issues with you at the MDDRP meeting on December 15, 2006.

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<sup>1</sup> “Protocol-specified” refers to protocol revision 8, as submitted in the PMA.