SUMMARY MINUTES

MEDICAL DEVICES DISPUTE RESOLUTION PANEL

December 15, 2006

Hilton Washington DC North
Gaithersburg, MD.

IMMUNOLOGY DEVICES PANEL MEETING
December 15, 2006

Attendees:

Chairman:

Scott D. Ramsey, M.D., Ph.D.
University of Washington School of Medicine

Industry Representative:

Melissa Walker, M.D., RAC
Stereotaxis, Inc.

Consumer Representative:

Allen A. Hughes, Ph.D.
George Mason University

Voting Member:

Jonathan D. Sackner-Bernstein, M.D., F.A.C.C.
Clinilabs, Inc.

Consultants:

Michael D. Crittenden, M.D.
Harvard Medical School

David DeMets, Ph.D.
University of Wisconsin

Warren K. Laskey, M.D.
University of New Mexico

Executive Secretary:

Nancy Collazo-Braier, Ph.D.

Ombudsman:

Les Weinstein, Esq.

CALL TO ORDER

Chairman Ramsey called the hearing to order at 8:03 a.m. and had the participants around the table introduce themselves. The meeting was being held at the request of Acorn Cardiovascular, Inc. to resolve a scientific dispute between the Sponsor and the Office of Device Evaluation in PMA P040049 for the CorCap Cardiac Support Device.

He read the Ombudsman's summary of the scientific issues in dispute, which describes the CorCap Cardiac Support Device as a non-resorbable polyester mesh implanted around the heart to provide ventricular support and reduce ventricular wall stress. It is indicated for patients with dilated cardiomyopathy who are worsening despite optimal medical management. On August 5, 2005, the FDA issued a not-approvable letter, citing lack of reasonable assurance of safety and effectiveness. Acorn amended the PMA with a post-hoc analysis to identify a sub-population in which CorCap CSD is safe and effective. FDA issued a non-approval determination to the amended PMA on February 2, 2006. The letter asked for clinical validation from a prospective study on the focused cohort. The Dispute Resolution Panel was charged with reviewing and making a recommendation to the CDRH Center Director as to the approvability of the PMA as amended.

Executive Secretary Collazo-Braier read the letters deputizing Drs. Ramsey, Sackner-Bernstein, DeMets, Laskey, and Crittenden as voting members for the duration of the meeting. She then read the conflict of interest statement. No waivers were issued.

OPEN PUBLIC HEARING

Mercedes K.C. Dullum, M.D., an investigator on the Acorn trial at Washington Hospital Center, said that she was impressed with the results she had seen in her CorCap patients. She had implanted 10 of the devices and urged the Panel to approve the device, since heart disease rates are rising and treatment options are few.

Robert D. Dowling, M.D., an investigator on the Acorn trial at the University of Louisville, said that he was impressed by the outcome of the device, which fills a gap in treatment options for patients who are not yet sick enough for a heart transplant or LVAD. He said the benefits of the treatment far outweigh the risk, adding that multiple operations are common in heart patients and that adhesions are easily managed.

SPONSOR PRESENTATION

Karen Becker, Ph.D., of Becker & Associates Consulting described the device and said that there was considerable science underlying the design, including lab studies, proof of concept studies, and animal models. She gave a history of the device from the beginning of the trial in 1999 through the granting of the appeal. She said that more information was available than was available to the Circulatory System Devices Panel (CSD), since the amended PMA provides data on potential investigator bias, supplemental information on safety at reoperation, extended follow-up on mortality, a postmarket study design for safety and long-term outcomes, post-hoc analysis of patients likely to benefit, and a revised indication for use based on ventricular size. There are also more data on the

imputation methodology used, a blinded validation of that methodology, and testimony from experts. She said that the data provides reasonable evidence of safety and effectiveness for the device and that the statistical methods applied to the trial are sound. The primary endpoint result was clinically relevant and beneficial. The secondary endpoint results support the hypothesis. The safety profile is reasonable in relation to the benefit. Since the original patient population adequately addressed safety and effectiveness questions, the focused cohort analysis was post-hoc and not necessary for approval.

Mariell Jessup, M.D., of the University of Pennsylvania, a member of the pivotal trial steering committee, summarized the CorCap Clinical study. The trial was a 300-patient, prospective, randomized controlled, multi-center trial. The control was continued medical therapy. Patients were accrued as two separate groups, those needing and not needing mitral valve repair (MVR). All patients were on optimal medical therapy for at least three months prior to randomization and throughout the trial. The median follow-up on the primary endpoint was 23 months. Of the three categories of outcomes: improved, same, or worsened, the treatment group had more patients improved and fewer worsened than the control group, statistically significant at a P value of 0.024, satisfying the primary objective of the trial. Treatment patients had fewer major cardiac procedures after the treatment than control, statistically significant at a level of 0.01. A greater percentage of patients in the treatment arm showed improved NYHA scores.

Regarding safety outcomes, she said that in 2004, 81.1 percent of treatment patients and 77.6 percent of control patients had serious adverse events. The numbers and types of events were not significantly different between the two arms. There were no device-related events. In 2005, 83.1 percent of treatment and 78.9 percent of control patients had had serious adverse events. There was a significant difference in mortality. She said that the device's reshaping effect allows the heart to function better. She said the secondary endpoints (left ventricular end diastolic volume, left ventricular end systolic volume, sphericity, Minnesota Living With Heart Failure Questionnaire and the SF-36) supported the primary endpoint, that the safety profile was acceptable, and that the conclusions provided a reasonable assurance of safety and efficacy.

Steven Piantadosi, M.D., Ph.D., of Johns Hopkins University, moderated the Sponsor's experts. He summarized the methodology of the expert review. Each expert independently reviewed the relevant data, documents, and literature. They all met and provided a consensus opinion and expert memorandum. He said that the primary pitfalls to avoid in interpreting the data are overly strict adherence to p-values as measures of evidence, taking subgroup findings as primary and definitive, deconstruction of the primary endpoint, misunderstanding the role of stratification, and misinterpreting the potential effects of missing data. The experts reached the conclusions that the primary endpoint was clinically meaningful, that a small amount of missing information does not compromise the result, that there is no evidence of bias affecting the primary endpoint, that the analysis of primary endpoint is in accord with proper statistical methods and the study protocol, that the results in MVR and no-MVR strata are clinically relevant, that results for the secondary endpoint are supportive, and that the device has a reasonable

safety profile, with benefits outweighing the risks. Although the study was surgical and could not be fully blinded, blinding was applied in the laboratories and in the aggregate results. He said that the primary endpoint was an appropriate composite and was statistically meaningful.

Donald B. Rubin, Ph.D. of Harvard University addressed statistics. He said that while there is data missing from the composite primary endpoint, multiple imputation is an appropriate way to address the problem and was suggested by the FDA. The missing data is the baseline core lab NYHA assessments for the first 174 patients of the total sample, 300. Though this is a good deal of missing data, it amounts to a small amount of missing information, between 9 and 2 percent, depending upon the model used. Multiple imputation is established as a valid method of dealing with missing data when a realistic model is used, and it includes uncertainty in its calculations. It assumes an "ignorable" missingness of data, but "ignorable" has a technical definition the CSD Panel members may not have understood. "Ignorable" missing data can be predicted from the observed data. Three criticisms of the model were voiced at the June 2005 meeting. First, there was too much data missing to be ignorable. Second, there were too few predictors included and those may have been improperly selected. Third, missing NYHA data was not normally distributed but ordinal. The first criticism was due to not understanding the technical definition of "ignorable." The second and third criticisms deserve consideration. However, after applying four new multiple imputation models, the criticisms are mitigated. Each of the four new MI models confirmed the conclusion of the PMA's MI model. There is a significant treatment effect of the CorCap relative to control on primary endpoint.

Randall C. Starling, M.D., MPH of Cleveland Clinic, an investigator and member of the steering committee, gave a clinical comment on the primary endpoint, which he said was statistically significant and clinically meaningful. Patients with the CorCap were more likely to feel better, evidenced by higher NYHA scores; had fewer transplants and ventricular assist devices; and showed no increase in mortality. Whether or not to perform major cardiac procedures (MCP) is decided by committee, so it is unlikely that bias would creep in. If it did and patients were not getting needed surgeries, heart failure and mortality rates in the treatment arm would have increased. The study showed a clinically meaningful endpoint with no demonstrable evidence of bias.

Dr. Piantadosi continued the discussion of primary endpoints, explaining the stratification used in the trial. Patients were stratified by MVR versus no-MVR in order to reduce the variance, control heterogeneity in the samples, and to balance the condition of the patients in the two arms of the trial. This was done to increase the precision of the results. Stratification does not require or dictate stratum treatment effects be part of the trial, since the goal of the study is to estimate the average relative treatment effects across the strata. Within both strata, however, CorCap is favored over control, and the treatment effect is clinically significant.

Dr. Piantadosi moved on to discuss secondary endpoints, starting with a statistical comment. The secondary endpoints were chosen for their clinical utility. They were

explicitly named as secondary outcomes, not primary. The protocol specified how they were to be analyzed, the timepoints, and the methodology, using longitudinal regression models. Proper interpretation of the secondary endpoints depends upon direction and magnitude of differences, not just p-values. Multiplicity adjustments are not necessary or required, since the purpose is to give supportive evidence to the primary endpoint. Secondary endpoints are not expected to independently establish safety or effectiveness. Variations in statistical significance are to be expected. The major secondary endpoints are supportive of the primary endpoint. A Hochberg adjustment was done in response to the FDA request to pre-specify a type I error rate. With the adjustment, LVEDV meets the collective success criteria. The treatment differences still favor CorCap.

Douglas L. Mann, M.D., of the Baylor College of Medicine spoke on the clinical relevance of the secondary endpoints. Secondary endpoints do three things. First, they reflect the mechanism of the device. The device decreases transmural stress, leading to reverse remodeling. The end diastolic and end systolic volumes show that the device is working as anticipated. Second, secondary endpoints should show fidelity with other devices doing a similar thing. The end-systolic and end-diastolic volumes reflect that. The third thing a secondary endpoint should do is show benefit to the patient. This is reflected in the questionnaire scores.

Steven F. Bolling, M.D. of the University of Michigan, a site PI during the study, and **Michael A Acker, M.D.** of the University of Pennsylvania, a member of the steering committee, spoke on safety, both perioperative mortality, and risk of re-operation. **Dr. Bolling** said that operative mortality in MVR CorCap patients was extremely low, less than 2 percent in already-ill patients. There were five deaths in the no-MVR stratum, one prior to the operation. The four perioperative deaths were hemodynamically unstable at the time of the surgery. These results were early in the trial. **Dr. Acker** explained that in very sick patients with low ejection fraction, the enlarged heart can become unstable during the operation. The deaths were reviewed in 2002, and it was decided to use cardiopulmonary bypass and intra-aortic balloon in patients with extremely enlarged hearts. After the meeting, the mortality rate dropped from16.7 percent to 3 percent. Adhesions were another safety issue to consider. While CorCap causes adhesions, adhesions are common to any surgery, and these adhesions do not affect safety. There were seven transplants in the CorCap group and no deaths in those patients. Of the 16 control patients with transplants, 2 died. The adverse event rates are similar to control. Since heart surgeons are used to adhesions, there is no evidence that adhesions have significant impact on patient outcomes.

Dr. Mann addressed the risk of pericardial constriction. There was no evidence of it in the animal models, no consistent echocardiograph evidence of it in patients, and no clinical evidence in the follow-up with the trial patients. Monitoring of the patients will continue out to five years.

Dr. Starling gave a clinical risk/benefit analysis. He said the device provides benefit, since the primary endpoint was met. It is safe, since the mortality rates are neutral and the secondary endpoints show a benefit. Functional class, quality of life, need for major

cardiac procedures (MCP), and heart size are all significantly improved. He concluded the presentation by pointing out that patients eligible for the device have few treatment options and that the device represented a therapy to address an unmet need.

FDA PRESENTATION

Aron Yustein, M.D., introduced the presentation. **Bram D. Zuckerman, M.D**., gave an introduction to the FDA review. He described the device and explained that the new indications--for use in adult patients who have been diagnosed with dilated cardiomyopathy, are symptomatic despite treatment with optimal heart failure medical management, have a dilated heart, and have a LVEF less than or equal to 35 percent or 45 percent if mitral valve repair or replacement is planned—were based on the post hoc focused cohort analysis. There are key disagreements between the FDA and the Sponsor on the history of the process. The primary endpoint for the Acorn trial was a composite of mortality, additional major cardiac procedures, and change in NYHA class, but 58 percent of patients did not have a blinded NYHA assessment at baseline. This is due to Acorn enrolling patients before the Sponsor and FDA had reached an agreement on the primary endpoint. Acorn changed its assessment method for blinded NYHA during the trial due to procedural and validity concerns. While FDA was in discussions with Acorn about these concerns, Acorn continued to enroll patients, leading to 172 patients being enrolled prior to the implementation of the new, blinded assessment.

FDA did not pre-specify imputation. Because the site and core lab NYHA assessments had poor agreement, FDA proposed imputation for the missing data. The Sponsor rejected the suggestion as clinically invalid. The Sponsor changed its position two months after being unblinded to the results.

Following the Advisory Panel vote of not approvable, Acorn proposed a reanalysis of the data to find a patient profile in which the risk benefit ratio was maximized. The FDA said the post-hoc analysis would be useful in generating a hypothesis for future studies and that post-hoc analysis would have to be prospective. When Acorn submitted the focused cohort analysis, it contained no new data, so a second non-approval letter was sent.

FDA's key concerns about the focused cohort submission are that the primary endpoint is not interpretable, the secondary endpoint results are problematic and not supportive of trial success, the safety concerns raised by the FDA and Advisory committee have not been adequately addressed, the risk-benefit profile is unacceptable in both strata, and a focused cohort analysis must be prospectively validated with additional clinical data.

William H. Maisel, M.D., MPH, Chair of the Circulatory System Medical Device Advisory Panel, summarized the June 22, 2005 Panel meeting. The Panel consisted of 15 participants of diverse relevant expertise. This Panel voted 9-4 not approvable. The Panel had a number of concerns: device effectiveness, both with primary and secondary endpoint issues; safety concerns; and concerns about missing data and subgroups. No one issue sank the application. The combined issues led to the determination of absence

of reasonable assurance of safety and effectiveness. In the primary endpoint, NYHA assessment was missing over half of the baseline data, MCP was possibly biased, and mortality was not statistically different from control. Dr. Maisel disagreed with the Sponsor's suggestion that the Panel did not understand imputation, noting that the Sponsor's statistician at the 2005 meeting had commented on the difficulty of making assessments with so much missing data. The bias in MCP is that the decision to operate or not is subjective. The reduction in mortality over the course of the study was encouraging but implied that there is a learning curve to the procedure. In the secondary endpoints, there were significant missing data, and the patients were not blinded. He noted that these were not end-stage, hopeless patients. One third of the control patients got better, so there is a danger of harming patients who may get better. The study was underpowered to detect important differences sufficiently to identify a subgroup that might benefit.

Ileana L. Pina, M.D., FACC, FAHA, FACP, gave the FDA clinical review of P040049. The primary endpoint was a composite of mortality, major cardiac procedure for worsening heart failure, and change in NYHA class. She elaborated on FDA's concerns with the PMA. For the interpretability of the primary endpoint, she questioned the validity of the NYHA measure and noted the 35 percent of patients missing outcome data. There was no observed benefit in mortality or NYHA. The MCP component in the no-MVR group is the only sign of potential clinical benefit, and it could be the result of bias and placebo effect. On the issue of secondary endpoints, she said that there is a lack of clinical or statistical significance in the majority of key structural and functional measures; there is a large amount of missing data for several secondary endpoints; the available objective data for functional endpoints actually favor the control group; and the correlation between changes in structure and function are low. The unaddressed safety concerns were the high (7.8 percent) perioperative mortality compared to control, dense adhesions and the related difficulty in reoperation, CorCap patient ineligibility for CABG, and possible future pericardial constriction. The risk/benefit profile was acceptable in neither strata. The focused cohort analysis may have identified a patient population with an better risk/benefit profile; however, this post hoc analysis would have to be prospectively tested.

Laura Thompson, Ph.D., gave a statistical review, focusing on the FDA's concerns with primary endpoints, secondary endpoints, and the focused cohort analysis. Because the trial was begun before the primary endpoint was agreed upon and the level of agreement between site-assessed NYHA and core lab NYHA was so low, there was considerable missing baseline information. FDA suggested multiple imputation for the missing data, to be accompanied by the primary endpoint analysis using complete data. The Sponsor chose to use imputation after the data was unblinded. It is important to decide on the analyses before unblinding to avoid bias. The device patients did have fewer patients with additional MCP, which is where the difference in primary endpoint occurs for the device. NYHA and mortality rates are not responsible for statistically significant results.

Secondary endpoints only matter if the primary endpoint was met, and the unblinding of the data prior to choosing a method of analysis calls that primary endpoint into question.

Of the secondary endpoints, only the p-value for LVEDV is statistically significant, according to the Hochberg procedure.

In the focused cohort analysis, the Sponsor identified a subgroup that may benefit from CorCap. The subgroup excludes high-risk patients. The same data is used to choose the cohort as to statistically test the cohort. This analysis cannot be the basis of an approval, since the perceived benefit can be chance or a Type I error. She showed how similar results can be found using data that shows no treatment difference between experiment and control.

Clyde W. Yancy, M.D., FACC, FAHA, FACP, a primary reviewer from the June 2005 meeting and a consultant to ODE, gave the perspective from that meeting. The fundamental question was whether surgically-induced remodeling achieved with the CorCap resulted in similar safety and efficacy as medically-mediated reverse remodeling. The NYHA and mortality portions of the composite primary endpoint were not helpful, and the trial was unblinded. Referral bias in the third portion of the endpoint concerned the first Panel. The original rationale for the device was that Class III and IV patients had few treatment options. Today, however, there are now several treatment options, many of which provide reverse remodeling. The premise was that surgical constraint of the left ventricle results in a decrement of LV size, reduces neurohormonal activation, reverses abnormal growth, and induces reverse remodeling. Reverse remodeling is associated with improved clinical outcomes. However, the surgical approach has not been established to result in beneficial reverse remodeling, since diastolic function can be harmed.

Many issues concerned the Advisory Panel in 2005. The Composite endpoint was achieved, but there was insufficient evidence of reverse remodeling, such as changed LV size, BNP change, or increased LVEF. They were concerned about bias, especially in the MCP category. There was a great amount of missing data. Labeling the device would also be difficult, since the Panel could not say the device saves lives, did not know the patient phenotype that responds to the device, had not seen convincing evidence of improved quality of life, and because it was unclear whether the need for transplantation or the referral for transplantation had been reduced in the study.

Since other treatment options exist, the hypothesis was not proven, the lack of convincing data, more data was needed before moving forward. That was the opinion of the Panel at the meeting.

Dr. Yustein returned to reiterate the FDA's concerns and close the presentation.

ACORN FOLLOW-UP/REBUTTAL

Dr. Becker gave the Sponsor's rebuttal. She reiterated that the original cohort provides valid scientific evidence to support approval of the product. The focused cohort study was not intended to stand alone. However, the PMA was modified at the FDA's

suggestion, and this Panel had data the previous Panel did not have. She said the Sponsor was flexible about the labeling.

Dr. Piantadosi reiterated the potentially misleading pitfalls he'd described earlier: overly-strict reliance on p-values where relative odds ratios can show treatment effect, taking subgroup findings as primary and definitive, deconstruction of the primary outcome, misunderstanding the role of stratification, and misinterpretation of the potential effects of missing data. He elaborated that missingness of data can be informative, depending on how it is used.

Dr. Mann addressed the question of CorCap's role in reverse remodeling. Reverse remodeling is a biologic surrogate for myocardial recovery. He said that the device does lead to reverse remodeling, but the trial was too small to show the mortality benefit. The beta blocker trial showed mortality benefit, but with 3000 patients. The device procedure should not be compared to SAVER or DOR procedures, since remodeling occurs at the molecular level. The pressure volume data is not consistent with pericardial constriction.

Dr. Becker gave examples of missing data in other heart failure device trials to demonstrate that the amount missing in this trial was actually less than in most studies.

The Panel asked why the Sponsor had changed its mind on using imputation. **Steven Anderson**, Acorn Regulatory Officer, explained that the initial refusal to use imputation was done hurriedly, based on input from statisticians who were not imputation experts. Input was limited because the regulatory affairs director and staff were still blinded. More information on imputation was obtained in July. The director was still blinded when the decision was made, in August.

FDA FOLLOW-UP/REBUTTAL

Dr. Matt Hillebrenner said that the FDA had sufficient statistical expertise and that the actions of the Sponsor or the FDA are not in dispute. He said the issue comes down to two questions: Do the overall treatment results justify placement of the CorCap concomitant with mitral valve surgery? and Do the overall treatment results justify performing a median sternotomy just to place the device? The FDA answers both questions in the negative. The trial has not shown safety and effectiveness.

Dr. Sackner-Bernstein asked about the FDA's concern about pericardial constriction. **Dr. Zuckerman** said that it was a possible safety concern that may arise later.

OPEN PUBLIC HEARING

Dr. Robert Brewer, M.D., of Henry Ford Hospital placed 10 of the devices during the trial. He said that the device is safe and effective, that significantly fewer CorCap patients require cardiac transplantation or a ventricular assist device, and that the device does not preclude future surgeries. He noted that the gold standard: heart surgery, transplantation, has a fifty percent median survival rate.

Eugene Grossi, M.D. of New York University had been asked by the FDA to comment, based on an editorial he wrote on the mitral valve strata of the trail. He spoke of mitral valve research. His clinical perspective on the device was that, although there was no difference in mortality, the patients with CorCap showed improvement in shape and end diastolic volume. He said that the study showed a clear benefit to surgical elimination of mitral regurgitation and an additional clinical benefit with CorCap.

OPEN COMMITTEE DISCUSSION

The Panel was charged to answer the following question: "Does the PMA as amended provide valid scientific evidence that demonstrates a reasonable assurance of the safety and effectiveness of the CorCap CSD for its intended use in the original patient population and/or the focused cohort?" In considering that recommendation, the Panel was asked to determine the following: "1) Whether the overall trial results for the primary effectiveness endpoint are interpretable and clinically meaningful, 2) Whether the secondary endpoint results are supportive of the safety and effectiveness of the device, 3) Whether FDA's safety concerns have been addressed by the data provided, 4) Whether the data submitted by Acorn adequately address FDA's safety and effectiveness concerns for the original patient population and/or focused cohort."

Dr. Sackner-Bernstein asked if the use of the missing at random assumption in the NYHA imputation was valid. **Dr. DeMets** said that the assumption was strong because the missing data was systemic. There are times in trials that patient characteristics change. When that happens, the assumption is bad. **Dr. Laskey** asked about the statistical robustness of the categories improved, same, and worsened. **Dr. DeMets** said that such endpoints are difficult to interpret.

Dr. Ramsey asked Acorn about the low degree of clinical benefit in the endpoints. **Dr. Mann** said that the primary endpoint shows good benefits if the primary endpoint is analyzed as a whole. **Dr. Jessup** added that simply not getting worse is a benefit to these patients, who are already on maximal therapy. **Dr. Starling** added that end diastolic volume and remodeling improvements improve over time, so long-term data will show more benefit. **Dr. Ramsey** further asked if the main driver of statistical significance in the primary endpoint was the change in major cardiac procedures. **Dr. Piantadosi** said that was true but that the primary endpoint was not designed to be deconstructed. **Dr. Ramsey** asked the FDA to respond. **Dr. Zuckerman** said that the Sponsor was referring to data outside of the scope of the meeting. **Dr. Hillebrenner** said that the FDA was not comfortable with the primary endpoint if the components could not be analyzed individually.

Dr. Sackner-Bernstein asked about the mortality confidence intervals. **Dr. Piantadosi** said that the risk ratios for control and device were equal, about 1.0. **Dr. Zuckerman** said the sample size was chosen to protect the primary endpoint but that the confidence interval was wide. **Dr. Thompson** added that it was not a time to event analysis.

Dr. Ramsey said that the primary endpoint is a composite of safety and efficacy data. He asked for more data on the potential bias in the category of MCP. **Dr. Mann** said that if patients had not received the procedures they required, there would have been more Class IV heart failures in the treatment arm. **Dr. Bolling** added that major heart surgery decisions are made by committee, so an individual's bias would be mitigated. **Dr. Thompson** showed data on the inconsistent NYHA measures. **Dr. Kubo**, speaking for Acorn, said that although NYHA is common, it is not standardized, so different clinicians score differently. In the core lab, the questions were standardized and made consistent; that is why the lab and site results were not comparable. The patient cannot be blinded to the questionnaire, but the assessor is blinded, since he or she does not see the patient.

Dr. Crittenden asked why ejection fraction did not improve. **Dr. Bolling** said that EF actually improved in CorCap patients and worsened in the control group, but the difference was not statistically significant. MVR patients also skew the results. **Dr. Crittenden** asked about the rings used in MVR surgery in relation to reverse remodeling. Dr. Bolling said the trial had been held before the rings were available, so any remodeling is due to the device or the surgery. **Dr. Laskey** asked if the association between treatment and outcome could be confounded by the site. **Dr. Acker** said there was no site difference.

Dr. Crittenden asked if the FDA had a response to Dr. Kubo's statement. **Dr. Pina** said that the FDA had struggled with trying to figure out what the core lab NYHA was measuring and the difference between the core lab and site assessments. **Dr. Mann** added that the assessor at the site was blinded and unable to see if there had been a surgery or not. **Dr. Piantadosi** said that any problem with the assessment would be equally present in the control group. **Dr. Zuckerman** disagreed.

Dr. Hughes asked if there was any difference between mechanical or biological valves in MVR patients. **Dr. Acker** said there was no difference between replacement and repair.

Dr. Sackner-Bernstein asked for the change in NYHA class over the trial in relation to the other components of the primary endpoint. **Dr. Zuckerman** said the trial tried to recruit Class III patients, but the core lab assessed 50 percent of the patients as Class IV. **Dr. Thompson** said he did not believe the relative difference between CorCap and control were the same in site NYHA compared to core lab NYHA. Additionally, patients who had a MCP did not have a final NYHA assessment. **Dr. Rubin** said **Dr. Thompson's** assessment was invalid, since it stratifies by outcome variables. **Dr. Thompson** said it did not affect the numerical result.

Dr. Sackner-Bernstein asked about the different imputation modes, wondering how using four different models affected the results. **Dr. Rubin** said that it can lead to increased variability, and sampling has to be done at the end of the calculations. **Dr. Pina** reiterated the differences between the site and core lab assessed patients.

Dr. Laskey noted that the majority of heart failure is related to coronary heart disease, and the trial had no coronary heart disease patients. He also noted that MVR complicated

the question of cause and effect in the study. **Dr. Ramsey** agreed that he could not tell if the MVR procedure and the CorCap device were additive, synergistic, or unrelated. **Dr. Sackner-Bernstein** commented that the procedure's risk for mortality is high.

Dr. Ramsey said that the amount of missing data that had to be imputed was extraordinary. **Dr. Hughes** said that after such data mining and complex calculations it is important to prospectively test the findings. **Dr. DeMets** said he was not troubled by the imputation so much as by the endpoints showing potential for bias and little difference between the device and control. **Dr. Sackner-Bernstein** found the missing at random assumption troubling.

Ms. Walker asked the Panel members if they could think of a patient subset that would potentially benefit from the therapy. **Dr. Ramsey** said the focused cohort was promising. **Dr. Sackner-Bernstein** said that the next step should be to plan a validation strategy for what the focused cohort analysis has shown. **Dr. Laskey** said that until the issue of the integrity of the parent trial was resolved it is difficult to make conclusions on subsets of the trial. **Dr. Ramsey** said that, despite the missing data, the secondary endpoints are the least subject to bias. **Dr. Laskey** noted the closeness of the control and treatment outcomes. **Dr. Sackner-Bernstein** said that the core lab NYHA methodology minimizes bias and adds consistency, but it should have been developed in one population and validated in another. Furthermore, the studies were cross-sectional, not longitudinal. In a best-case scenario, it could not be more than 60 percent accurate.

FDA SUMMATION

Dr. Donna-Bea Tillman said that Acorn has not provided sufficient valid scientific evidence to support approval. To determine that Acorn has demonstrated reasonable assurance of effectiveness, the Panel would have to find that the device would provide a clinically significant result in a significant portion of the target population. In this trial, the results of the primary endpoint analysis are not interpretable, and the secondary endpoints do not demonstrate a clinically meaningful benefit. The perioperative mortality associated with the device cannot be outweighed by the benefit, since none was shown. The focused cohort should be viewed as hypothesis-gathering and would require additional prospective data to test the hypothesis. This data-gathering must be pre-market, and the FDA is willing to work with the company in that process.

SPONSOR SUMMATION

Dr. Piantadosi said that the study and the primary endpoint were designed to be responsive to clinical concerns and methodological rigor. Although there are internal irregularities in the primary endpoint, the endpoint itself was met and demonstrates substantial consistency in effect. While there is a chance of bias, the investigators did everything possible to mitigate that. Imputation is not the first choice, but the multiple imputation models demonstrate that the outcomes are not sensitive to method of imputation. Though the data is imperfect, it is high-quality and reasonable evidence.

Dr. Jessup said that the risk of surgery is outweighed by the benefit of avoiding transplant, VADs, and deteriorating clinical status, especially if the device and procedure is held to the same standard as other heart procedures.

Dr. Paintadosi said that is a mistake to break the primary endpoint into its components, but if it is broken down, one must note the 41 percent decrease in the need for transplantation as a benefit. He reiterated that the decision on transplantations could not have been due to bias.

Dr. Rubin pointed out that for the missing at random assumption, the assumption was used in comparing the treatment and control, which had the same data missing due to the time of the NYHA assessor change. He added that some of the FDA's analyses were not valid by FDA standards. There is evidence that the device is needed and little that it is unsafe.

PANEL DELIBERATION AND VOTE

Dr. Ramsey asked the industry and consumer representatives if they would like to comment. **Ms. Walker** said the voting members should consider whether or not there were other opportunities to explore patient sub-populations that might be proposed in conditions. She also said that the labeling could be made as narrow as is necessary to mitigate the Panel's concerns. **Dr. Hughes** pointed out that the physician is a learned agent and that approving the device would give the physician another tool. However, using the device precludes certain future procedures. He said that biocompatibility and biointegrity must be considered. He also noted that the control group seemed to do better than treatment on some secondary endpoints. He raised issues of avoidable risk, avoidable consequences, and avoidance of future heart transplants.

Dr. Sackner-Bernstein said that the surgical intervention had a high mortality risk, though how high was unclear. He said index hospitalization should be counted, since CorCap patients had longer stays. Perhaps the advantage of the device is not that it prevents heart surgery but that it allows the time of the surgery to be chosen.

Executive Secretary Collazo-Braier read the Panel recommendation options for pre-market approval applications, including the thresholds and definitions of these possible recommend options. **Dr. Ramsey** called for a motion. **Dr. Crittenden moved to recommend approvable with conditions. Dr. Laskey seconded the motion**. **The Chairman** called for conditions of approval. **Dr. Crittenden moved as a condition of approval that the Sponsor continue the proposed post hoc analysis and that the FDA work with the Sponsor to narrow the labeling.** He asked for his fellow-panelists' help in narrowing the labeling. **Dr. Sackner-Bernstein** asked that the condition be narrowed to a single condition. **Dr. Crittenden** restated his first motion, that the Sponsor continue the post hoc analysis, though he said it may be better to narrow the labeling first. **The motion was not seconded, and seeing no one willing to second it, the Chairman closed the discussion and called for a new motion.**

Dr. Laskey moved to recommend approvable with conditions. Dr. Crittenden seconded the motion. Dr. Laskey moved that the condition be continued enrollment in a clinical trial with better safety estimates in order to give more assurance that it is a safe procedure in the patient population. **Ms. Walker** asked for clarification of the motion. **Dr. Laskey** said that he wanted to see better safety results than have been presented, a lower perioperative 30 day rate that shows steadily decreasing mortality. **Chairman Ramsey** observed that if more or better PMA data were needed to approve the application, the application would not be approvable, so the condition may have been invalid. **Dr. Crittenden** asked whether the motion called for new data or for clarification of existing data, and **Dr. Laskey** said his motion called for new data. **The Chairman** called for a second on the condition. **There being no second**, he asked for other conditions to the motion to approve with conditions. No conditions were named, and for the sake of procedure, he called the vote to recommend approvable with conditions, though no conditions had been voted upon. **The vote was 3-1 to oppose the motion, with Dr. Crittenden voting in the affirmative. The Chairman** called for other motions.

Dr. Sackner-Bernstein moved to recommend that the application is not approvable. Dr. Laskey seconded the motion. Dr. Ramsey opened the floor for discussion. **Dr. Hughes** said that a vote of not approvable is harsh but that post-market surveillance cannot substitute for a pre-market condition. He said that a prospective study is needed, which cannot be done post-market, due to regulations. **Ms. Walker** said that any previously-unseen data should be reviewed and analyzed before the application is declared non-approvable. **Dr. Ramsey** agreed that the Panel recommended that the FDA follow up on unseen data. **Dr. Sackner-Bernstein** agreed that the recommendation of non-approvable was harsh but there was too much uncertainty about safety and benefit for the regulations to allow approval. Any therapy is decided upon after weighing risk and benefit. In this case, they could not be weighed, due to the uncertainty. **Dr Laskey** said that although the Panel members were sympathetic to the investigators, the safety concerns could not be overlooked. **Dr. Crittenden** pointed out that the patients needing the device were at risk if no action were taken as well. He said that the device was probably easier for surgeons to approve and that a symptomatic benefit and avoidance of secondary procedures had been shown. The **Dr. Ramsey** called for further discussion. Hearing none, he called the question. **The motion carried 3-1 with Dr. Crittenden voting in opposition.**

Dr. Ramsey asked each member to explain his vote. **Dr. Laskey** said that he did not see the safety signal that would allow him to overlook the ambiguity on efficacy. **Dr. Sackner-Bernstein** said that there was not enough efficacy data to outweigh the lack of safety data. **Dr. DeMets** said that he was not convinced, due to doubts about the primary outcome and the size of the trial. **Dr. Crittenden** said that some efficacy had been shown in the reduced need for LVAD placement and cardiac transplants. With expert surgeons, this would be a safe procedure, especially for patients with few alternatives. **Dr. Weinstein** thanked the Panel members, the Sponsor, and the FDA for their work.

Dr. Ramsey polled the members on what would make the PMA approvable. **Dr. Laskey** said there would have to be another trial, though the current data could be included through a Bayesian design. **Dr. Sackner-Bernstein** said that the studies should be designed to put the upper confidence interval of safety in an acceptable range and give convincing evidence of a clinically meaningful benefit. **Dr. DeMets** said the existing data had been fully analyzed, that a new trial was necessary, that the new trial should address bias issues that arose in this trial, and that the new trial should be larger. **Dr. Crittenden** gave no further comment. The **Dr. Ramsey** thanked the participants and **adjourned the meeting at 4:47 p.m**.

I certify that I attended this meeting of the Medical Devices Dispute Resolution Panel on December 15, 2006 and that these minutes accurately reflect what transpired.

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Nancy Collazo-Braier, Ph.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Scott D. Ramsey, M.D., Ph.D.
Chairman

Summary Prepared by

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