

ACORN'S EXPLANATIONS AND CLARIFICATIONS REGARDING ACORN'S UNRESOLVED OBJECTIONS TO ODE'S PANEL PACK -- November 9, 2006

PLEASE NOTE: The Ombudsman was unable to resolve, between FDA's Office of Device Evaluation (ODE) and Acorn, several objections made by ODE to certain portions of Acorn's Panel Pack as well as several objections made by Acorn to certain portions of ODE's Panel Pack. As a result, he is allowing ODE to explain and/or clarify any unresolved objections and Acorn to explain and/or clarify any unresolved objections.

The following are Acorn's explanations/clarifications:

1. Acorn's position is that the analysis plan in Protocol Revision 8 (with imputation) provides the protocol-specified method for analyzing the primary composite endpoint, via the intent-to-treat principle and with multiple imputation for missing data. Acorn objects to ODE's assertion -- raised for the first time in this MDDRP proceeding -- that Protocol Revision 6 and not Revision 8 provides the protocol-specified analysis plan.

Acorn objects to ODE's claim that Revision 6 is the operative protocol. In summary:

a. Revision 8 is the protocol relied on by ODE itself for their review of the PMA and administrative decisions, including: the ODE decision to file the PMA; ODE's PMA review and analysis prior to the 2005 panel meeting; ODE's presentations at the June 2005 meeting of the Circulatory System Devices Advisory Panel; ODE's not approvable letters; and the Ombudsman's Summary of Scientific Issues in Dispute.

b. ODE has never objected to Acorn's use of Revision 8 until this MDDRP proceeding began.

-- It is unacceptable for ODE to claim now, at this late stage in the history of this PMA, that Revision 8 is not the operative protocol for protocol-specified analysis.

-- Both ODE and Acorn have been using Revision 8 all along. It is the version that requires use of multiple imputation for missing data, an analysis which has been discussed extensively by both parties and presented at the 2005 Panel meeting.

c. The IDE submission history for Revision 8 is clear:

-- ODE's letter of May 19, 2004, regarding IDE supplement 44, recommended eight changes to the Revision 7 protocol including multiple imputation for missing baseline data;

-- Acorn responded to ODE's request on May 28, 2004, in IDE Supplement 45; in this submission, Acorn agreed to six of the eight recommended changes and asked FDA for more information about the use of multiple imputation; Acorn's agreement with ODE's recommendations initiated a revision in the protocol from Revision 7 to Revision 8;

- ODE sent Acorn an IDE unconditional approval letter on July 1, 2004 (thereby approving Rev 8). Within this letter, ODE made a general statement regarding NYHA analysis methodology that did not provide the clarification about multiple imputation that Acorn had requested;
- Acorn submitted IDE Supplement 47 on August 6, 2004, stating that Acorn would perform multiple imputation for missing core lab data as suggested in ODE's May 19, 2004 IDE conditional approval letter ("Rev 8 with imputation"). Acorn did not submit a revised protocol at this time because Rev 8 had already been unconditionally approved by ODE on July 1, 2004;
- FDA's Michael Berman (lead reviewer on the PMA) telephoned Acorn on August 17, 2004, to say that no formal correspondence will be sent by FDA regarding IDE supplement 47 (that is, Rev 8 with imputation); no formal correspondence was needed, because FDA had already issued an unconditional approval letter for the IDE;
- PMA is submitted on December 20, 2004, including Revision 8 protocol as an Attachment.

d. The Revision 8 protocol-specified method (original PMA, Attachment H, page 808) is as follows:

"Core lab assessment of NYHA classification is performed throughout follow-up, blinded to treatment group, at six-month intervals beginning with the 6 month follow-up visit. However, the core lab assessment was instituted after the trial had started, and is available for only 126 patients at baseline. Therefore, to calculate change in NYHA, multiple imputation was used to estimate a core lab-assessed NYHA for the patients who were missing this score at baseline. The primary endpoint was then analyzed using core lab NYHA assessments for all patients at both baseline and during the last available follow-up prior to the common closing date."

e. ODE has stated its agreement that the method applied by Acorn to handle missing data at baseline is statistically valid and appropriate: "After further analysis, FDA believes that Acorn's primary endpoint analysis is robust and that technical questions about the imputation methods are now a secondary concern." Email from Donna-Bea Tillman, Ph.D., Director of ODE, to Steve Anderson, Acorn, on June 1, 2006.

2. ODE's letter of May 19, 2004, plainly stated that ODE considered certain analyses of the primary endpoint "not acceptable to use," and ODE's July 1, 2004 letter advising Acorn it could perform a range of analyses must be interpreted consistently with the May letter's warning that certain analyses would be "not acceptable."

a. ODE's letter of May 19, 2004, paragraph numbered 1, stated: "For primary analyses, it is not acceptable to use two unblinded assessments or to use one blinded and one unblinded assessment."

b. In this letter, the references to "blinded" assessment and "unblinded" assessments are the references to the NYHA core lab assessment and the NYHA site assessment. "Site-to-core" comparison is the way Acorn refers to a comparison of unblinded site NYHA assessment to blinded core lab NYHA assessment.

c. ODE's warning in May that certain analyses are "not acceptable to use" for the primary analyses is a specific warning that necessarily placed a limitation on ODE's more general recommendation in its July 1, 2004, letter that Acorn analyze the NYHA portion of the primary composite endpoint using "as many methods as you believe to be appropriate in order for you to make a sound conclusion regarding the effectiveness" of the device.

d. Thus, ODE's May letter already stated that certain analyses would never be appropriate because they were "not acceptable," and those analyses did not become acceptable by ODE's July letter. ODE never stated that it was reversing its prior determination on unacceptability of certain analyses.

3. Acorn's clarifications of Table 1 in ODE's paper on Acorn Cardiac Support Device (Panel Pack page 11), and ODE's Statistical Memorandum Table 2.

a. ODE's Table 1 in its paper entitled Acorn Cardiac Support Device fails to state that the line "Imputing the Missing Baseline Core Lab NYHA" is the protocol-specified method in Revision 8 for analyzing the primary composite endpoint. The additional analyses presented by ODE are sensitivity analyses.

ODE also fails to state this as the protocol-specified method in its Statistical Memorandum, Table 2.

b. Revision 8 is the protocol that has been used by both Acorn and ODE in presenting all analyses from the date the PMA was filed through the presentations at the prior Panel meeting and through the not approvable letters. In connection with preparation of the Panel Pack for this MDDRP, ODE claims, for the first time, that Revision 6 is the protocol that ODE believes should be used as the protocol-specified method for analyzing the primary endpoint. Acorn objects for the reasons stated above.

c. ODE's analysis for "Patients with an Outcome for Primary Endpoint" is inaccurate, and is inconsistent with ODE's May 23, 2005 Review Memorandum (page 22, Table 3).

Based on ODE's May 23, 2005 Review Memorandum, this line should read:

| <u>Analysis Description:</u> | <u># Pts.</u> | <u>Odds Ratio (95% CI)</u> | <u>p-value</u> |
|---|---------------|----------------------------|----------------|
| Patients with an Outcome for Primary Endpoint | 191 | 1.84 (0.94, 3.59) | 0.07 |

ODE now asserts that the above information from its May 23 Review Memorandum was incorrect because it included time period as a covariate, and that its revised analysis removes time period. ODE also claims that the time-period covariate does not help with the primary endpoint inference, but this is incorrect, as shown below.

ODE states that the time-period covariate is defined such that all patients in time period 1 (which ended before introduction of the NYHA core-lab instrument) were, by definition, excluded from the available-cases analysis unless they were worsened by virtue of death or qualifying MCP. While this is true, it does not justify the removal of the covariate from protocol-defined analysis. ODE claims that the covariate does not help with inference; to the contrary, ODE's own analysis shows that it does, since the new version of the available-cases analysis differs substantially from the old version. For this reason, the protocol-defined analysis, including the time-period covariate, should be employed.

4. ODE's references to "clinically meaningful success criteria" are irrelevant, because they are referring to concepts discussed in connection with negotiations to select a primary endpoint in connection with Revision 3 of the protocol (submitted May 9, 2001). These endpoints were not selected and the statements to which ODE refers are unrelated to the interpretation of the primary composite endpoint that was selected subsequently.

a. ODE refers in various places in its Panel Pack to so-called "clinically meaningful success criteria," including: in its paper entitled Acorn Cardiac Support Device discussing secondary endpoints (text above Table 4 and in Table 4) and below Table 9; in ODE's Clinical Summary Memorandum Sections XI.B, XII, and XIII; and in its Panel Pack Attachment 10. Acorn objects to these references.

b. The "Clinically meaningful success criteria" that FDA references were proposed in IDE supplement 19 submitted on May 9, 2001 and were part of the Revision 3 protocol included in that submission. The clinical success criteria proposed in Revision 3 were tied to structural and functional endpoints which constituted the primary efficacy endpoints and were used as a benchmark to calculate sample sizes in Revision 3.

Once the primary endpoint was changed to a composite endpoint in Revision 6, the clinical success criteria tied to the primary endpoint in the Revision 3 protocol were no longer relevant. The clinical success criteria proposed in Revision 3 do not appear in any other approved protocol (Revisions 2, 6, or 8); thus, neither Revision 6 nor Revision 8 included them. Nor were they discussed in the PMA or utilized in support of any PMA analyses. Nor were they presented to the Circulatory System Devices Advisory Panel in June 2005.

c. In addition, in IDE Supplement 19, Acorn clearly noted that there are no universally accepted or validated definitions for "clinically significant" as a caveat to engaging in the exercise of trying to specify "clinical success criteria" at FDA's request.

5. Acorn objects to ODE's inclusion of meeting minutes (for a July 19, 2005, meeting) which were revised by ODE to include statements attributed to Dr. Clyde Yancy (who participated by phone) but which Dr. Yancy never made during the meeting.

a. ODE's version of the minutes is in summary form in the document entitled History of Events for P040049 and in Attachment 24 of ODE's Panel Pack.

b. Acorn believes that ODE's version of the minutes is false in that they do not record what was said during the teleconference.

c. ODE's History of Events document purporting to summarize the meeting states (page 75), "Meeting minutes generated by Acorn, reviewed by FDA", and thus misleadingly suggests that Acorn agrees to the minutes, which Acorn does not. In addition, ODE's Attachment 24, by using Acorn's letterhead for the ODE-modified minutes, falsely and misleadingly suggests that these are Acorn's minutes or implies that Acorn agrees with the revised minutes, which is wrong.

d. A consultant to Acorn who attended the meeting (who is a former branch chief of ODE/CDRH) has confirmed to Acorn his recollection that Dr. Yancy never said during the meeting the statements that ODE inserted into the meeting minutes.

e. Attached to this document are Acorn's minutes of the July 19, 2005 meeting.

Memorandum

To: Matt Hillebrenner

From: Janell Colley

Subject: CorCap CSD PMA P040049
Minutes from Meeting between FDA and Acorn Cardiovascular Staff
Held on 19 July 2005

Date: (DATE)



FDA

Bram Zuckerman, MD, Division Director
Dina Fleischer, Branch Chief
Matt Hillebrenner, Lead Reviewer
Ileana Pina, MD, Consultant to FDA
Julie Swain, MD, Consultant to FDA
Laura Thompson, PhD, Biostatistician
Eric Chen, MS, DCD
Wolf Saperstein, MD
Clyde Yancy, MD, Advisory Panel Lead Reviewer
Michael Berman, PhD, Senior Reviewer

Acorn

Spencer Kubo, MD, Global Medical Director
Steve Anderson, VP Corporate Assurance
Lisa Wipperman Heine, Regulatory Director
Heidi Hinrichs, Clinical Director
Janell Colley, Regulatory Manager
Scott Brown, PhD, Biostatistician
Russ Pagano, Regulatory Consultant

Background

The referenced meeting was conducted to discuss the concerns expressed by FDA and the Advisory Panel at the meeting on 22 June 2005, specifically to review the proposal submitted to FDA by Acorn on July 15, 2005.

FDA indicated that Acorn's proposal was interesting, but that other elements would be necessary to get to the goal line. FDA and Acorn expressed the same goal: to use available data to demonstrate reasonable safety and effectiveness for the CorCap CSD.

FDA sees the items in Acorn's proposal described as "Key issues/concerns" (items 1-6 on page 1) *and* those described as "opinions expressed by the Panel" (items 1-4 on page 2) as being equally important issues. In addition, FDA believes that there are other important areas that may need to be addressed.

Overall, FDA emphasized that Acorn would need to provide compelling evidence demonstrating that the proposed indicated patient subgroup is truly that cohort that derives the greatest benefit within appropriate risk parameters. FDA indicated that evidence of clinical benefit/clinical utility should be a major part of the additional analyses. FDA acknowledged that additional analyses would not be perfect

Discussion

The discussion focused on several key themes; discussion pertaining to each theme is summarized in the following sections.

Additional Analyses Demonstrating the Most Appropriate Subgroup

Acorn reviewed their first proposal (item A page 2) related to limiting the patient population; FDA inquired as to how the LVEDD and Peak VO₂ parameters were selected since the cut points did not match the values seen in the patients who had experienced operative death.

FDA observed that if these parameters (LVEDD and Peak VO₂) are predictors for mortality, it would be interesting to examine what the predictors of benefit would be using a continuous variable approach.

Acorn emphasized that the patients who were excluded based on LVEDD and Peak VO₂ were indeed worse off and the remaining subset showed an overall increase in the efficacy signal.

FDA expressed interest in seeing data that points to predictors of safety and efficacy before agreeing to a specific subpopulation; they suggested that analyses of 12-month Peak VO₂ and LVEDDi vs. mortality be conducted, including data plots that confirm the proposed hypothesis.

FDA indicated that within the scope of low EF, peak VO₂ is a predictor of mortality; they inquired as to whether pts. w/ low Peak VO₂ might potentially gain more benefit even though they may be at higher risk and suggested that a greater risk might be worth a greater benefit.

FDA confirmed that a qualitative review of available data would be the goal of these additional analyses, rather than a statistically pure examination as they are now looking for consistent signal that is clinically relevant.

FDA indicated they would like sensitivity analyses performed to show that the correct cut points were chosen for the subgroup analyses.

FDA questioned whether the patients who had been excluded were early enrollees; Acorn indicated that while a few more patients in the exclude cohort were early enrollees, there was essentially not a meaningful difference in enrollment time between the included and excluded patient cohorts.

FDA observed that it might be possible to show more benefit in higher risk patients, and reiterated their interest in seeing predictors of safety and efficacy to evaluate the most appropriate patient cohort for the CorCap.

FDA asked about whether Acorn had examined wall motion abnormality as a predictor of success; Acorn offered that most patients in the cohort were globally hypokinetic and indicated that a “responder/non-responder” analysis could potentially examine these questions further, with the caveat that a 300 pt. population is difficult to subdivide.

Heart Failure-Related Hospitalization

One of the additional concerns identified by Dr. Clyde Yancy at the Panel meeting was lack of data specific to heart failure-related hospitalizations; Dr. Yancy reiterated this concern and stated that this is an important measure for a contemporary heart failure trial.

FDA recommended that hospitalization data be examined to compare congestive heart failure (CHF)-related re-hospitalization rates between treatment and control groups. In order to do this, FDA and Acorn will need to come to agreement on the definition of a CHF-related re-hospitalization. FDA agrees with Acorn that baseline hospitalization does not need to be factored into this comparison. FDA suggested a standard KM approach looking at death or 1st CHF hospitalization.

FDA recommended that Acorn look at SSED from Contak CD PMA for ideas on how this data has been analyzed and reported.; in this way, Acorn could potentially align the CorCap trial with other CHF trials.

Acorn expressed concern that CHF hospitalization has only lately been adopted in prophylactic ICD trials as an endpoint, and that this endpoint had not been prospectively identified as a required endpoint, nor uniformly appropriate for all CHF trials.

FDA indicated that each trial must stand on its own merits, and that since the Acorn trial had not shown more definitive results, there was a need at this time to look at additional data. Dr. Yancy pointed to both overall hospitalization and time to 1st CHF hospitalization as important parameters for clinicians to judge patient benefit over the longer term. Acorn and FDA will need further discussion regarding definitions, methodology, and committee adjudication.

FDA stressed that because of the problems identified with this trial, particularly related to the risk/benefit ratio, Acorn should consider presenting CHF re-hospitalization data, and also suggested methods for presenting CHF re-hospitalization data to get hospitalization data without using a committee.

Surgical Questions/Issues

FDA expressed interest in seeing operative time and blood loss for all patients who had reoperations, including OUS patients.

Acorn and FDA discussed the possibility of arranging a teleconference so that FDA and Acorn surgeons could discuss questions about reoperation; a sample FDA question for study surgeons was whether any infiltration into the myocardium had been seen in CorCap patients.

Additional sensitivity analysis of imputation for missing baseline NYHA

FDA offered that while concern had been expressed at Panel about missing data and the use of imputation, FDA's impression of the imputation was that it added value to the overall analysis of the CorCap.

FDA requested that Acorn do another sensitivity analysis of the imputation of missing baseline NYHA data involving a re-sampling, non-parametric, distribution free model similar to the suggested analysis for missing Peak VO₂.

Provide OUS data

FDA inquired as to whether Acorn's had OUS data that could be used as confirmation of the results seen in the US trial. OUS data could be valuable to support the US trial hypothesis.

Acorn observed that the patient population in the OUS included a wider variety of presenting symptoms and additional concomitant treatments that would confound this examination. However, Acorn indicated that mortality and safety data could be examined in the US trial. In addition, predictors of overall mortality rather than operative mortality could perhaps be identified by looking at interactions terms, although this type of analysis would be difficult in a 300 patient cohort.

FDA inquired as to the possibility that OUS data may provide additional information to support US data, and expressed an interest in seeing not only less risk to patients, but also more benefit.

FDA stated that to further augment the US trial results, Acorn would need to do additional analyses with either the current data or historical controls; ideally, FDA is looking for another database that is more prospective in nature.

Dr. Yancy cautioned FDA and Acorn about the use of OUS data since other countries have a much different approach to CHF than the US

FDA indicated that the pertinent question is whether OUS data can be extrapolated to US, and that if FDA has confidence in EU data, they will consider its on its own merits.

Analyses of Peak VO2 data at 6 & 12 months imputing missing data

FDA suggested doing an analysis of missing Peak VO2 data by using an imputation model that assumes missing for cause. (need to consider treatment assignment in imputation).

When FDA inquired as to the possibility of bringing patients back to complete exercise testing, Acorn emphasized that this would be problematic since patients have all passed the 12 month window. Acorn pointed out that the rank analysis used to look at exercise testing presented in the PMA already represented an alternate analysis method for handling missing data.

FDA reiterated that w/regard to Peak VO2, FDA is interested in identifying which patients will derive greatest the benefit from CorCap.

Proposed Changes to Labeling

Acorn reviewed proposed changes to labeling; FDA indicated that these changes would be negotiated when the appropriate patient population could be identified and agreed upon.

FDA inquired as to the appropriate indication for this device, and suggested that it be an idiopathic, cardiomyopathic population, optimally medically managed, with a wide QRS.

Both Acorn and FDA physicians indicated that to specify QRS width in the CorCap indications was not necessarily valuable, and suggested a layered therapy approach that would allow flexibility for physicians and patients. In order to communicate this in the labeling, it was suggested that the indications refer to an “optimally managed patient” which would cover drug therapy and other device therapy.

Post Approval Study

Acorn presented information on their proposed increased sample size for the post approval study, with an emphasis on ischemic enrollment.

FDA indicated that an increase was a good idea, but that Acorn would need to propose an even larger sample size.

FDA indicated that changes to the post approval study were more appropriate to discuss after the appropriate patient population had been identified and agreed upon, and that Acorn should apply its resources first into the demonstration of safety and efficacy of the CorCap, emphasizing that the concern about ischemic patients was not central to the additional analyses that must be conducted.

Conclusion

FDA mentioned that Dr. Yancy would continue his involvement in the on-going review of the PMA. In addition, FDA indicated that from an administrative point of view, the review cycle clock is ticking and that Acorn should propose a timeline to which FDA can react based on time needed for review of additional analyses. Specifically, FDA offered the following three options for possible administrative/regulatory pathways:

- Disapproval
- Major Deficiency Letter
- Fast Response From Acorn Allowing FDA To Work Within Current Review Cycle (We Are At Day 65 Or So)

FDA and Acorn reviewed the “action items” identified, which included the following:

1. Additional analyses demonstrating that the proposed exclusions are appropriate and offer the best risk/benefit profile (e.g., choose different peak VO₂ and LVEDDi; look at mortality vs peak VO₂ and LVEDDi, etc.)
2. Examine other secondary endpoints within identified subgroup
3. Examine re-hospitalization to determine rates of CHF hospitalizations in treatment and control groups.
4. Conduct additional sensitivity analysis of imputation for missing baseline NYHA
5. Present OUS data to help provide an independent dataset that may shed light on safety and efficacy of US trial; present data in same manner as panel pack to the extent possible.
6. Conduct additional analyses of Peak VO₂ data at 6 & 12 months (impute missing data, show cumulative frequency curves, etc)
7. Arrange a teleconference w/FDA Acorn and surgeons (discuss questions from Drs. Swain and Saperstein)