Testimony to the FDA's Circulatory System Devices Panel on the Premarket Approval (PMA) Application P100045 for the CardioMEMS Champion HF Monitoring System
Michael A. Carome, M.D., and Sidney Wolfe, M.D.
Public Citizen's Health Research Group
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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group, testifying on behalf of myself and Dr. Sidney Wolfe, the founder of our group. We have no financial conflicts of interest.

On December 8, 2011, Public Citizen testified before this panel, strongly opposing approval of the PMA for the CardioMEMS Champion HF Monitoring System (the CardioMEMS System), primarily because the design and conduct of the single pivotal clinical trial evaluating the device had multiple features that created readily apparent bias concerning the effectiveness endpoints, favoring the experimental group.[1] A majority of the voting members of this panel reached a similar conclusion.[2] In particular, on the question of whether there was a reasonable assurance that the device was effective, seven members voted no, and three voted yes.

In January 2012, the FDA issued a "not approvable" letter to the sponsor, requesting additional data to demonstrate that there is a reasonable assurance of effectiveness of the device.[3] The agency appropriately recommended that a new, prospective clinical trial be conducted to assess the effectiveness of the CardioMEMS system.

CardioMEMS — unfortunately with FDA agreement — instead opted for a series of post hoc ancillary analyses of data from a subset of surviving subjects enrolled in the original pivotal clinical trial. These analyses have numerous limitations and flaws that undermine their validity, and they are not an adequate substitute for a well-designed, prospective randomized clinical trial. The new data presented by the sponsor fail to provide sufficient evidence to conclude that there is reasonable assurance that this first-in-class, permanently implanted medical device is effective.

Problems with the single, randomized pivotal trial

For the randomized pivotal trial, the primary effectiveness endpoint was the rate of heart failure-related hospitalizations through six months.[4] Secondary effectiveness endpoints included the following:[5]

(1) Change from baseline in pulmonary (PA) mean pressures

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[1] Carome MA, Wolfe S. Testimony to the FDA's Circulatory System Devices Panel on the premarket approval application (PMA) for P100045 CardioMEMS Champion HF Monitoring System. December 8, 2011. http://www.citizen.org/documents/testimony-on-cardiomems-champion-hf-monitoring-system.pdf. Accessed October 8, 2013.

[2] Food and Drug Administration. FDA executive summary for the October 9, 2013, meeting of the Circulatory Systems Devices Panel. Page 1. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370689.pdf. Accessed October 8, 2013.

[3] *Ibid*. Page 9.

[4] Food and Drug Administration. FDA executive summary for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf. Accessed October 8, 2013.

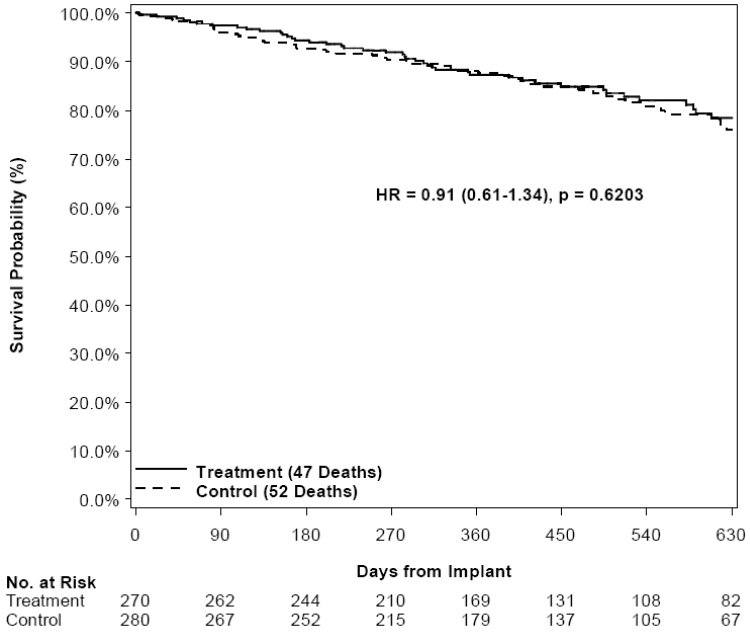
[5] *Ibid*. Page 16.

(2) Proportion of subjects hospitalized for heart failure
(3) Days alive outside of the hospital
(4) Total quality of life score on the Minnesota Living with Heart Failure Questionnaire

While statistically significant differences were seen in each of the pre-specified primary and secondary effectiveness endpoints, as well as many other supplementary endpoints, the absolute differences between the treatment and control groups for several endpoints — such as days alive without heart failure hospitalization — were relatively small.[6]

Also, there were no statistically significant differences in mortality outcomes between groups over the duration of the study (see figure below) and no statistically significant difference in all-cause hospitalization rates at six months (0.88 events/subject/6 months in the treatment group and 0.96 events/subject/6 months in the control group; p = 0.4065[7]).

Figure: Kaplan-Meier Survival Plot Over the Study Duration[8]



Several features of the design and conduct of the study created readily apparent bias in favor of the treatment group. Thus, it is highly plausible that the differences seen in the effectiveness endpoints

[6] *Ibid*. Pages 12-26.
[7] CardioMEMS, Inc. CardioMEMS Heart Failure Monitoring System briefing document, prepared for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 75. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM281523.pdf. Accessed October 8, 2013.
[8] Food and Drug Administration. FDA executive summary for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 29. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf. Accessed October 8, 2013.

were due in large part or even entirely to bias, rather than the device itself. The most prominent and egregious source of bias in the pivotal trial were the subject-specific treatment recommendations provided to individual site clinical investigators by nurses employed by the sponsor for treatment group subjects only.[9] However, other important sources of bias included the following:

(1) Single-blinded study design: This is one feature of the study design contributing to study bias that was unavoidable. Nevertheless, clinical investigator awareness of each subject's study group assignment may have influenced decisions regarding both medical therapy and whether to hospitalize a subject, both of which would directly affect the primary and secondary effectiveness endpoints.

(2) Consultation with the national principal investigators (PIs) regarding medical management of treatment group subjects only: Per protocol, clinical investigators at each of the study sites were encouraged to consult with the national PIs — who likely were nationally recognized experts in the management of congestive heart failure — "to optimize the success of medical management of PA pressures."[10] Apparently, no such encouragement for consultation was provided with respect to the medical management of control subjects, whose care might have been enhanced had the site clinical investigators consulted with the national PIs with the same frequency as for treatment group subjects.

(3) Unbalanced content and frequency of telephone contacts between investigators and treatment group subjects versus control group subjects: The protocol included scripts for telephone contact with subjects in both study groups. The scripts were identical except for subject-specific medication adjustments that occurred in the treatment group in response to PA pressure data.[11] Whenever a telephone contact occurred with a treatment group subject, a control group subject was randomly selected to receive a matching phone contact.[12] These were not comparable study interventions because treatment subjects received telephone contacts that were based on contemporaneous subject-specific clinical information (i.e., PA pressure information) and included medication changes. Control subjects, on the other hand, received random, generically scripted calls unrelated to any pertinent contemporaneous contextual clinical information that may have warranted medication changes. Furthermore, the mean number of telephone contacts per treatment

[9] Food and Drug Administration. FDA executive summary – addendum, prepared for the December 8, 2011 meeting of the Circulatory System Devices Panel. Pages 2-4. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282272.pdf. Accessed October 8, 2013.

[10] Food and Drug Administration. FDA executive summary for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 52. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf. Accessed October 8, 2013.

[11] CardioMEMS, Inc. CardioMEMS Heart Failure Monitoring System briefing document, prepared for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 38. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM281523.pdf. Accessed October 8, 2013.

[12] *Ibid*. Pages 38-39.

group subject was slightly higher than the mean number per control group subject (3.0 ± 2.3 versus 2.5 ± 1.8).

Bias is very insidious and can influence investigators' actions and judgments. Once a study is completed, it is impossible to prove how much of a difference between study group outcomes resulted from bias and how much was from an actual difference between the interventions being tested. In this case, multiple features of the pivotal study design and conduct created readily apparent bias and prevented any valid conclusions from being drawn about the effectiveness of the CardioMEMS System.

Problems With the New Ancillary Analyses

The sponsor conducted multiple ancillary analyses of longitudinal follow-up data from subjects who had been enrolled in the randomized pivotal trial (Part 1) and had survived and not dropped out. During this follow-up study (Part 2), pressure data from the CardioMEMS implanted device were made available to the physicians for all subjects. A number of comparisons were made to assess effectiveness, including the following, among others:[13]

- Comparison of heart failure (HF) hospitalization rate in former control group subjects (n=170) to the rate seen in control group subjects during the randomized trial (n=280)
- Comparison of the HF hospitalization rate in former treatment group subjects (n=177) to the rate seen in treatment group subjects during the randomized trial (n=270)
- Comparison of the HF hospitalization rate in former control group subjects to the rate seen in former treatment group subjects
- Comparison of the change in HF hospitalization rate between the randomized study and the follow-up study for the control subjects versus the treatment subjects.

Although the results of these analyses consistently suggest that access to the CardioMEMS pressure data reduced the HF hospitalization rate, several factors highlighted by the FDA undermine the validity of these analyses.

In particular, FDA reviewers noted the following:

- These analyses "are considered ancillary [not primary] analyses because no study success criteria could be defined a-priori and because the study was not originally designed with these analyses in mind…Caution should be used when interpreting the results because the study is not powered for these analyses, multiple analyses were conducted on the same data, and preservation of Type I error was not attempted."[14]

[13] Food and Drug Administration. FDA executive summary for the October 9, 2013, meeting of the Circulatory Systems Devices Panel. Pages 15-19. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370689.pdf. Accessed October 8, 2013.

[14] *Ibid*. Page 15.

- 93 of 270 (34%) treatment group subjects and 110 of 280 (39%) control group subjects randomized into the pivotal clinical trial did not enter the follow-up study (Part 2). Bias in the ancillary analyses may have been "introduced due to the non-random exiting of subjects prior to onset of Part 2. It appears that the subjects who exited in the Control group were similar to those who exited in the Treatment group with respect to their baseline characteristics (as measured at the start of Part 1). However, the clinically important covariates were not collected at the beginning of Part 2, which started a mean time of approximately 525 days after the baseline covariates were measured. It is possible that the values of some important covariates changed from Part 1 to Part 2. Using Part 1 baseline values for those covariates in the proposed combined data analysis approach may not be appropriate. Furthermore, because of the lack of the covariates at baseline of Part 2 study, FDA was not able the evaluate:
  1. if the subjects in Part 1 and Part 2 were comparable after subjects exited from the duration of Part 1;
  2. if important covariates between the comparison arms remained balanced in Part 2; and
  3. if subjects in Part 2 study still met the trial inclusion/exclusion criteria."[15]

- "It is not possible to evaluate…whether the difference in clinical outcome [in the ancillary analyses] may be confounded with differences in the subject populations."[16]

- "The mortality in Treatment groups changed from 18.5% in Part 1 to 17.5% in Part 2. This similarity in mortality is expected since the Former Treatment group continued to have access to PA pressures. The mortality in the Control groups decreased from 22.9% in Part 1 to 12.4% in Part 2. Although a decrease in mortality was expected in the Control groups due to PA data availability in the Former Control group, one would have expected the rate to be similar to that of the Treatment group in Parts 1 and 2, approximately 18%. The fact that the mortality rates in the Former Control group is 12.4% versus 17.5% in the Former Treatment may suggest a difference in the patient populations in Part 2 of the study."[17]

On this last point, it is inappropriate of the FDA to suggest that a decrease in mortality was expected in the former control group subjects due to PA data availability in light of data from the pivotal trial showing no evidence of a mortality benefit in subjects in the treatment group.

Even if these ancillary analyses were valid, we agree with the FDA's current view that "the clinical significance [of any reduction in heart failure hospitalization] is less clear."[18] This is particularly true given the absence of any survival advantage and the apparent lack of a sustained quality-of-life benefit at 12 months in the treatment group in the randomized pivotal clinical trial.

[15] *Ibid*. Pages 24-25.
[16] *Ibid*. Page 41.
[17] *Ibid*. Page 25.
[18] *Ibid*. Page 41.

Conclusions and Recommendation

In summary, Public Citizen strongly recommends that to protect public health, the FDA should not approve the PMA application for the CardioMEMS System because:

(1) The design and conduct of the single pivotal clinical trial evaluating the CardioMEMS System had multiple features creating readily apparent bias with respect to the effectiveness endpoints in favor of the experimental group, thus preventing any valid conclusions from being drawn regarding the effectiveness of the device;
(2) Every ancillary analysis had serious limitations and flaws that prevent valid conclusions from being drawn about the effectiveness of the CardioMEMS system.
(3) As a result of (1) and (2), there are insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh the risks related to the implantation procedure.

Public Citizen urges the advisory committee to recommend that the FDA again disapprove the PMA for the CardioMEMS System until a well-designed randomized clinical trial, without the aforementioned biases, is conducted. It is our view that the FDA conclusion presented at the December 2011 meeting is still valid: "The CHAMPION trial does not provide an unbiased estimate of the effect of the device. It is not clear what if any effect in the study is due to the device itself. Further, the effect of the device in a real real-world setting (if this device were to be approved) is unknown."[19]

[19] FDA slide presentation at the December 8, 2011 meeting. Slide 111. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM284020.pdf. Accessed October 8, 2013.