Testimony to the FDA Circulatory System Devices Panel Regarding the CardioMEMS Champion HF Monitoring System: Insufficient Evidence of Benefit

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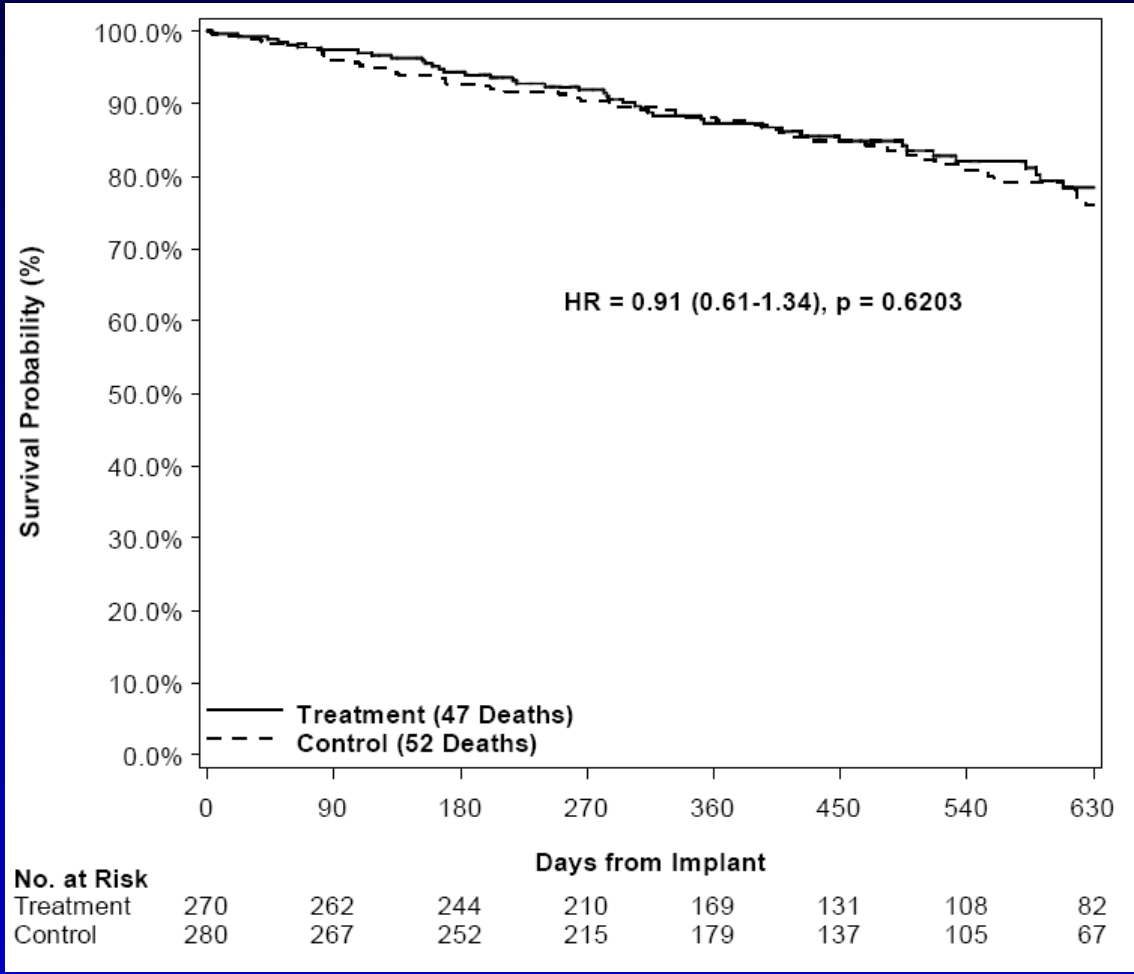
(We have no financial conflicts of interest)

CardioMEMS Randomized Pivotal Trial

- Primary effectiveness endpoint: heart failure-related hospitalizations through six months.
- Secondary endpoints included:
  - Change from baseline in pulmonary (PA) mean pressures
  - Proportion of subjects hospitalized for heart failure
  - Days alive outside of the hospital
  - Total quality of life score on the Minnesota Living with Heart Failure Questionnaire

Mortality Outcomes with the CardioMEMS System – Pivotal Trial



CardioMEMS Pivotal Trial Conduct Created Bias in Favor of the Treatment Group

- Subject-specific treatment recommendations provided to individual site clinical investigators by nurses employed by the sponsor for treatment group subjects only
- Single-blinded study design
- Consultation with the national principal investigators regarding medical management of treatment group subjects only
- Unbalanced content and frequency of telephone contacts between investigators and treatment group subjects versus control group subjects

Ancillary Analyses of CardioMEMS Data

- 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 rates between the randomized study and the follow-up study for the control subjects versus the treatment subjects.

FDA-Identified Limitations and Flaws of Ancillary 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."**

FDA-Identified Limitations and Flaws of Ancillary Analyses (cont.)

- "Furthermore, because of the lack of the covariates at the 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."

FDA-Identified Limitations and Flaws of Ancillary Analyses (cont.)

- **"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.**

FDA-Identified Limitations and Flaws of Ancillary Analyses (cont.)

- **"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."**

Recommendations

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 that all created 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;

Recommendations (cont)

(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 is 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.

Conclusion

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."