

## **FDA Executive Summary - Addendum**

Prepared for the  
December 8, 2011 meeting of the  
Circulatory System Devices Panel

P100045

CardioMEMS *Champion*<sup>™</sup> HF Monitoring System

CardioMEMS, Inc.

### **Introduction**

FDA has additional information to provide to the Advisory Panel. This information was not present in the PMA submission. This addendum provides information FDA obtained based on inspections conducted by the Division of Bioresearch Monitoring (BIMO). Based on the additional information obtained, FDA drafted this addendum and shared it with the sponsor. The sponsor was also given the opportunity to write an addendum of their own, and it is being provided to the panel.

### **Background**

BIMO inspections revealed an issue that FDA believes is important to bring to the Panel's attention. The issue pertains to the sponsor's and the national Principal Investigators' involvement in the management of individual enrolled subjects. This issue may have bearing on the interpretation of the results of the study.

The approved protocol allowed the sponsor to review pulmonary artery (PA) pressure readings and to alert investigators if the pressure readings were elevated. The investigators (or designees) were to manage the enrolled subjects. The following is an excerpt from the protocol (page 15 of 58).

“The Investigator or designee will review the PA pressure measurements from the home monitoring unit. Alert limits are automatically set as described in Appendix E. The Investigator or designee will be alerted by CardioMEMS, if those parameters are exceeded. If the PA pressures are elevated, the Investigator or designee should make medication changes according to the recommendations in Appendix E.”

Appendix E is attached to this addendum; it was also previously sent as an appendix to FDA’s initial Executive Summary, starting on page 51.

## **Additional Information**

### Medical Therapy Recommendations from Study Nurses

FDA acknowledges that heart failure therapy recommendations based on PA pressure readings for Control group subjects were not allowed according to the protocol. However, nurses working for the sponsor made medical therapy recommendations for heart failure management for specific subjects during the course of the trial. Medical therapy recommendations from the study sponsor were limited to Treatment (i.e. investigational) group subjects only. As a result, FDA is concerned is that this study tested a treatment strategy of device plus heart failure recommendations vs. optimal medical therapy alone, which was not FDA’s understanding of the original intent of this trial.

According to inspections of study-related documents, the sponsor contacted investigational sites during the trial regarding recommendations for Treatment group subjects with respect to starting, stopping and/or titrating specific heart failure medications, including doses, intervals and duration. FDA’s inspections did not include all clinical sites. However, the sponsor provided FDA with copies of what the sponsor terms “email alerts” from all clinical sites. FDA reviewed a sample of the email communications between the sponsor and the clinical sites. Please note that telephone communication occurred between the sponsor and the investigational sites. FDA has no documentation of the content of telephone discussions and, consequently, no way to assess the impact of therapy recommendations made via telephone.

FDA acknowledges that all medical therapy adjustments were implemented by the investigators and not by the sponsor.

Specifically, FDA notes the following:

- The sponsor made recommendations based on prior subject-specific responses.

- The sponsor made recommendations regarding the discontinuation of medications that the sponsor thought were disadvantageous.
- Recommendations for changes in medications that were beyond the scope of Appendix E were made based on PA pressure readings (for example, sildenafil).
- While the sponsor did recommend evaluating appropriate study subjects for sleep disorders through study-wide communications, the sponsor recommended evaluating specific Treatment group subjects for sleep disorders via email communications to investigational sites. Evaluating the effect of treating sleep disorders was not part of the study protocol.
- The sponsor suggested the use of outpatient IV diuretics; please note that the primary effectiveness endpoint was limited to inpatient hospitalization events.

Examples of such communications, which were sent to clinical investigators via email, include the following:

On 5-7-2008, a CardioMEMS nurse wrote recommendations that include “PAD > 20: Consider increasing the loop diuretic. If patient responding to current Lasix dose, increase to 40 BID; if not currently responding to Lasix dose, increase to 80mg QD. IF no response consider adding PRN thiazide or switching to Demadex if bioavailability a concern.”

On 6-6-2008, a CardioMEMS nurse wrote recommendations that include “Titrate loop diuretic as needed for elevated PA pressures. Recent upward trend in PA pressures suggest a need for more diuretic. Screen for sleep apnea and refer for sleep study if positive. Patient at high risk due to large size. (Sleep Apnea Screening tool attached.) Confirm patient is not using NSAIDS. Encourage a STRICT 2gm sodium, 2000ml Fluid restricted diet.

On 10-30-2008, a CardioMEMS nurse wrote recommendations that include “PCWP 14 suggests increased volume- Consider increasing Lasix to 40mg BID or switching to Demadex if bioavailability a concern with Lasix. Consider using PRN Thiazide to facilitate diuresis. Up-titrate Diovan to optimal dose as tolerated (160mg BID). Add Hydralazine and Nitrates to current regimen uptitrating as tolerated. Evaluate patient's current compliance with treatment of his Obstructive Sleep Apnea. Consider re-evaluation of patient's Sleep Breathing Disorder diagnosis (OSA vs Central Sleep Apnea) and options for treatment.”

On 12-12-2008, a CardioMEMS nurse wrote “What is your plan for management of [specific subject]? Implant hemodynamics (PA 68/41(52) PCWP 30 CO 1.5

PVR 14.67) suggested increased volume with a PCWP 30 in addition to PAH with a PVR 14.67. Addition of Ismo 40mg QD on 10/2/08 appears to have helped with a decrease in PAM from 43 to 31. She is on maximum medical therapy (ARB, BB, Nitrate, Aldactone, Digoxin, Diuretic) at this point. Would you consider challenging her with Sildenafil in addition to adjusting her diuretic regimen by switching to Demadex or possibly using outpatient IV diuretics?"

On 12-26-2008, a CardioMEMS nurse wrote "I wanted to alert you that [specific subject]'s mean pressure went from 27 on 12/24 to 53 on 12/26. Do you think this warrants her to take an extra dose of diuretics today? It is the holidays and we expect pressures to increase, but we still want to prevent her from going to the hospital."

On 12-29-2008, a CardioMEMS nurse wrote "I wanted to alert you of an increasing trend in the mean of [specific subject]. Although his mean pressure trend remains relatively flat, his pressures have an upward trend. We are seeing several patients in the trial experience post-holiday rise in pressures most likely due to dietary indiscretion and medication noncompliance. Do you think this patient would benefit from a few days of increase diuretic until his pressures return to baseline? I also noticed that this patient is on Metformin in the face of renal insufficiency (SCr 1.4) which may be contributing to difficulty in managing his volume status."

On 8-21-2009, a CardioMEMS nurse wrote "I wanted to alert you to [specific subject]'s increase in pressures over the past week with a mean of 42 today. She responded nicely to extra Lasix back in May. Would you consider this again?" A response the same day from the physician, directed to the site nurse but including the CardioMEMS nurse, states "agree give extra dose for 3 days and check if anything different in terms of diet, activity, etc."

#### Medical Therapy Recommendations from National Principal Investigators

The national Principal Investigators (PIs) provided medical therapy recommendations for heart failure management for specific subjects during the course of the trial. The following examples illustrate this interaction.

On 11-16-2007, one of the national PIs sent the following email to CardioMEMS after talking with the principal investigator at a specific site. "I spoke with [the site principle investigator] this morning. We had a very collegial and productive discussion about hemodynamic monitoring, in general, and his patients, in particular. It sounds like patient #2 is very ill and will likely be made DNR.

Patient #3 has had persistent elevation in her PA pressures, despite escalation of diuretic dose. Following [CardioMEMS employee]'s conversation with [the site principle investigator] yesterday, he increased the furosemide dose from 80 mg bid to 120 mg bid (the patient was previously [prior to 10/25] on 40 mg bid). The patient does not have any clinical signs of extra-cellular fluid volume excess. The patient does, in fact, have substantial mitral regurgitation. I suggested that he consider starting a long acting nitrate and letting me know what happens; we may need to back off of the diuretic, if the nitrate works. I also thanked him for his great and ongoing contribution to the study."

On 5-7-2008 a CardioMEMS nurse wrote "There are a few of your patients whose PA pressures are trending upward or are borderline elevated. I have reviewed the following cases and would like to review with you the plan for medical management. I know my information may not be current/accurate so please update as appropriate. If you or [the site principle investigator] would like further consultation with one of the national PI's or member of the steering committee I would be glad to arrange that."

Please note, the approved protocol does allow this type of interaction. "Consultation with the national PI's is encouraged to optimize the success of medical management of PA pressures." (page 48 of 58 of Appendix E)

The sponsor's addendum includes analyses in tables 1-3 showing the number and impact of treatment recommendations made by the sponsor via email. FDA has not verified these analyses and is unaware of how they were conducted. In addition, interactions between the sponsor and the clinical sites were not limited to email contact, and included interactions by telephone. The sponsor's analyses do not assess the impact of telephone interactions.

*FDA Commentary:*

The sponsor was aware of the randomization assignment of subjects and made treatment recommendations to investigational sites for subjects assigned only to the Treatment group. The national principal investigators reviewed individual subjects with site investigators and made specific treatment recommendations. The sponsor told FDA that these interventions were intended to ensure compliance with the protocol, and clearly some of the interventions recommended by the sponsor are consistent with Appendix E of the approved protocol. While FDA acknowledges that the sponsor bears responsibility for ensuring compliance with the protocol, the level of interaction between the sponsor and the clinical investigators regarding individual subjects' treatment plans was inconsistent with FDA's expectations based on the protocol. FDA is concerned that the heart failure recommendations by the sponsor and National PIs for individual study subjects in the Treatment (investigational) arm only may bias the study results because these efforts may minimize hospitalization for Treatment group subjects without a comparable effort for Control group subjects. Additionally, FDA is concerned that the level of involvement of the sponsor during the clinical trial would not be duplicated in a post-market environment.

FDA will ask the Panelists to provide a discussion of the significance of these findings with respect to the introduction of bias in the study results, interpretability of the study results, and the applicability of the study results to a post-market environment.

## Additional Question

FDA is concerned that the conduct of the clinical trial may have biased the study results. Inspections coordinated by FDA's Division of Bioresearch Monitoring (BIMO) identified evidence that the sponsor, who had knowledge of the randomization assignment, or the principal investigators routinely contacted investigational sites and made specific therapeutic recommendations for some Treatment Group study subjects, including

- titration of medication doses,
- addition or discontinuation of medications,
- recommendations for outpatient intravenous medication administration,
- the addition of medications that were not included in the protocol, and
- sleep study evaluations not included in the protocol.

FDA is concerned that the study results may be biased by these recommendations because investigators did not receive similar treatment recommendations from the sponsor for Control Group study subjects. FDA's interpretation of the protocol is that therapeutic changes were to be made by the study site investigators.

**The information obtained through inspections coordinated by FDA's Division of Bioresearch Monitoring raises concerns for FDA that specific therapeutic recommendations may have minimized heart failure hospitalizations for Treatment Group study subjects without an equivalent impact for Control Group study subjects. FDA is concerned that the study results may be biased and that the ability to interpret study results may be compromised by the trial conduct.**

- FDA is concerned that the specific treatment recommendations made by the sponsor may have introduced bias into the study results. Please discuss whether or not you agree with this concern.**
- If the specific treatment recommendations introduced bias into the study results, please discuss how this impacts the ability to interpret the study results.**
- FDA is concerned that the measures taken by the sponsor would not be duplicated in a post-market setting, if the device were to be approved. Please discuss how the difference between how the study was conducted and how the device would likely be used in a post-market setting should be taken into account when interpreting the study results.**
- The information identified in the BIMO inspections was not submitted by the sponsor as part of the PMA. Please discuss whether this information is relevant to an evaluation of the safety and effectiveness of the device.**

## APPENDIX E: MANAGEMENT OF HEMODYNAMIC PARAMETERS

The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations. The unique nature of the implanted device allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures. The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

### Guidelines for managing heart failure using pulmonary artery pressures

The CHAMPION trial will differ from previous hemodynamic monitoring studies in that specific recommendations will be made to utilize pressures in heart failure management including use of diuretics and vasodilators.

#### Pulmonary Artery Pressure Goals:

PA Systolic	15 - 35 mmHg
PA Diastolic	8 - 20 mmHg
Mean PA pressure	10 - 25 mmHg

An elevation of pressures beyond these reference ranges should be considered a volume overloaded status. Diuretic therapy should be adjusted to reduce these pressures to within pressure goals unless the following occurs:

1. Serum creatinine increases by 20%
2. If systemic systolic blood pressure drops by 20 mmHg when changing from supine to a standing position
3. Symptomatic systemic hypotension

The above listed clinical events should be confirmed by three (3) evaluations in order to prevent withholding the appropriate treatment regimen.

If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed. If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated. If the pressures remain high after the above steps are taken, then the reference ranges may be reset for the individual patient and the new values should be considered "optivolemic". Medication adjustments and patients' responses must be documented prior to changing the goal ranges.

Diuretics and vasodilators should be adjusted based on the subject's baseline diuretic requirement, knowledge of the subject's prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline. Consultation with the national PI's is encouraged to optimize the success of medical management of PA pressures.

A decrease in the pulmonary pressures below the established ranges should be considered a volume depletion event and diuretic therapy should be held and chronic dose should be lowered.

**In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.**

### **Opti-volemic**

#### **Opti-volemic Definitions**

- Subject symptoms: minimal symptoms and minimal evidence of poor perfusion
- Invasive Hemodynamic Monitoring:
- Pulmonary artery systolic pressure 15 – 35 mmHg
- Pulmonary artery diastolic pressure 8 – 20 mmHg
- Pulmonary artery mean pressure 10 – 25 mmHg
- HF Pressure Measurement System Parameters:

The initial parameters will be set to the above values. After all guidelines for managing HF using pulmonary artery pressures as described on the previous page have been implemented and documented, the Investigator may reset the values to an acceptable range for individual subjects and establish the range in mmHg in the secure website.

#### **Opti-volemic Treatment Recommendations**

- No medication changes based on hemodynamic data obtained from the HF Pressure Measurement System
- Baseline chronic aggressive therapy (reduced LVEF)
  - a. ACE inhibitor (ARB or other vasodilator if ACE not tolerated) to target dose
  - b. Digoxin, diuretic and electrolyte replacement advised
  - c. Consider spironolactone as indicated in subjects with stable renal function and potassium handling
  - d. Nitrates to appropriate doses as tolerated
  - e. Beta-blocker administration and/or uptitration according to guidelines when subject is not hypervolemic.

If the subject has signs of poor perfusion (cold), consider other interventions, such as:

- a. Admission for monitoring and further adjustment of medical management
- b. Intravenous (IV) pharmacotherapy
- c. Increase vascular volume if still without evidence of congestion at rest
- d. Consider invasive hemodynamic monitoring for determination of Cardiac Output if indicated

### **Hyper-volemic**

#### **Hyper-volemic Definitions**

- Subject symptoms: Congestive symptoms (wet)
- HF Pressure Measurement System Parameters: above the pre-determined opti-volemic range
- Daily trends: elevated trend data outside the pre-determined opti-volemic range
- Weekly trends: elevation in trend data

#### **Hyper-volemic Treatment Recommendations**

- Add or increase diuretic (and appropriate electrolyte replacement)
  - a. Increase or add loop diuretic
  - b. Change to another loop diuretic
  - c. Add thiazide diuretic (with caution)
  - d. IV doses of loop diuretic
  - e. Serum electrolyte evaluation with change in baseline medication
  - f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic
- Add or increase nitrates
- Start or re-educate in salt intake and fluid restriction
- If subject has signs and symptoms of poor perfusion (cold) in addition to being hyper-volemic:
  - a. Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
  - b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

### **Hypo-volemic**

#### **Hypo-volemic Definitions**

- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- HF Pressure Measurement System Parameters: below the pre-determined opti-volemic range
- Daily trends: decrease in trend data outside the pre-determined opti-volemic range
- Weekly trends: decrease in trend data

Hypo-volemic Treatment Recommendations

- Lower or discontinue diuretic
  - a. If on a thiazide diuretic with loop diuretic, lower or discontinue the dose of thiazide (and adjust electrolyte replacement)
  - b. If on only loop diuretic, lower the dose or discontinue
  - c. Consider liberalization of oral fluid restriction and salt restriction
- If postural hypotension, hold or lower vasodilators and/or oral nitrates, especially if hypotensive when sitting or supine
- If worsening renal function, hold or lower ACE/ARB dose, especially if hypotensive
- If subject had signs and symptoms of poor perfusion (cold) in addition to being hypo-volemic:
  - a. Consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring or the use of IV therapeutic agents
  - b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

**Recommended Frequency of HF Pressure Measurement System Review**

Subject Status	Weekly	At least 2– 3 times per week until optivolemic	At least 2 – 3 times per week until pressure stabilizes
Opti-volemic	X		
Hyper-volemic		X	
Hypo-volemic		X	
Medication modifications			X
Significant deviations in trend data			X