

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL

MEETING

March 1, 2007

**Hilton Washington D.C. North
Gaithersburg, Maryland**

Circulatory System Devices Advisory Panel Meeting

March 1, 2007

Attendees

Chairperson

William H. Maisel, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Voting Members

Sharon-Lise Normand, Ph.D.
Harvard School of Public Health
Boston, Massachusetts

Richard L. Page, M.D.
University of Washington School of Medicine
Seattle, Washington

John C. Somberg, M.D.
Rush University Medical Center
Lake Bluff, Illinois

Consultants

Eugene H. Blackstone, M.D.
Cleveland Clinic
Cleveland, Ohio

Jeffery S. Borer, M.D.
Cornell University
New York Presbyterian Hospital
New York, New York

Jeffrey A. Brinker, M.D.
The Johns Hopkins Hospital
Baltimore, Maryland

Michael J. Domanski, M.D.
National Institutes of Health
Bethesda, Maryland

Gregory A. Ewald, M.D.
Washington University School of Medicine
St. Louis, Missouri

Paul J. Hauptman, M.D.
St. Louis University School of Medicine
St. Louis, Missouri

Norman S. Kato, M.D.
Cardiac Care Medical Group
Encino, California

John R. Teerlink, M.D.
San Francisco Veterans Affairs Medical Center
San Francisco, California

Industry Representative

Marcia S. Yaross, Ph.D.
Biosense Webster, Inc.
Diamond Bar, California

Consumer Representative

Mike Fleming, D.D.S., P.A.
Dentist
Durham, North Carolina

Executive Secretary

James P. Swink
Food and Drug Administration
Rockville, Maryland

FDA Participants

Bram Zuckerman, M.D.
Director, Division of Cardiovascular Devices

Nilsa Loyo-Berrios, Ph.D.
Epidemiology Branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics

Randall Brockman, M.D., FACC
Division of Cardiovascular Devices, Office of Device Evaluation

Matthew Hillebrenner, MSE
Division of Cardiovascular Devices, Office of Device Evaluation

George Koustenis, M.A.
Division of Biostatistics, Office of Surveillance and Biometrics

CALL TO ORDER AND INTRODUCTORY REMARKS

Chairperson William H. Maisel, M.D., M.P.H., called the meeting to order at 8:00 a.m. He noted that the voting members present constitute a quorum.

Panel Executive Secretary James P. Swink read the conflict of interest statement. A full waiver has been granted to Gregory A. Ewald, M.D. He then read statements appointing Eugene H. Blackstone, M.D.; Jeffrey A. Brinker, M.D.; Michael J. Domanski, M.D.; Gregory A. Ewald, M.D.; Paul J. Hauptman, M.D.; Norman S. Kato, M.D.; Jeffery S. Borer, M.D.; and John R. Teerlink, M.D. as temporary voting members.

Dr. Maisel asked the panel members to introduce themselves.

FIRST OPEN PUBLIC HEARING

No members of the public asked to speak.

SPONSOR PRESENTATION

David M. Steinhaus, M.D., Vice President and Medical Director, Cardiac Rhythm and Disease Management Division, Medtronic, discussed some of the history of the Chronicle Implantable Hemodynamic Monitoring (IHM) System and introduced the rest of Medtronic's presenters.

Lynne Warner Stevenson, M.D., Harvard Medical School, discussed the role of congestion resulting from elevated filling pressures in acute heart failure and the need for reliable outpatient assessment of elevated filling pressures.

Philip B. Adamson, M.D., Director, The Heart Failure Institute at Oklahoma Heart Hospital, described the Chronicle IHM and discussed early clinical experience. He said the IHM Guided Care plan implemented in the non-randomized Phase I and II studies was found to positively impact heart failure morbidity in ambulatory patients.

Robert C. Bourge, M.D., Heart and Vascular Research Center, University of Alabama at Birmingham, described the COMPASS-HF study. He concluded that the totality of the clinical experience provides reasonable assurance of the safety and effectiveness of continuous hemodynamic monitoring in management of heart failure.

Dr. Steinhaus said a training plan had been developed, and he described the sponsor's proposed condition of approval study. Although he acknowledged they did not meet the primary effectiveness endpoint in COMPASS-HF, Dr. Steinhaus said the clinical experience validates the physiologic basis and clinical impact of volume management using intracardiac pressures and that consistency provides reasonable assurance of the safety and effectiveness of the device.

Dr. Borer asked about the apparent discrepancy in the overall mortality presented. **Ven Manda, Medtronic**, said the data in the panel pack was only through six months of follow-up while that presented went beyond six months. Dr. Borer then asked about data on the predictive value of pressure measurements in the control group. Mr. Manda said it was intended to gauge the accuracy of an automatic detection algorithm which was not part of the PMA approval, but he said it was included because it was a pre-specified secondary endpoint.

Dr. Page asked about communication between the device and the external device which correlates barometric pressure with that measured by the device. Dr. Bourge said the data is correlated when the patient interrogates the device with the remote monitoring device. Dr. Page next asked why there is no option for active fixation and how that interferes with placement. **Charles J. Love, M.D., Ohio State University**, said the pressure sensor's design ruled out the extendable retractable helix, and they chose the tined lead over a fixed exposed helix because more implanters are familiar with it. He also said after gaining experience the dislodgement rates dropped significantly. There were two instances of entrapment, but there were no sequelae and the leads were left in position and abandoned.

Dr. Page inquired further about the removal traction required to extract a lead that has been in place for some time given that the stylette is four centimeters short of the tip of the lead. Dr. Love said that the lead is well constructed and in two out of three or four cases he needed to use a stylette; in the other extractions the leads pulled right out. He also noted that the position of the lead in the outflow tract helps prevent fibrosis from occurring and plastering the lead against the wall of the ventricle.

Dr. Somberg was troubled by the different durations and composite endpoints presented and hoped for consistent data on the number of patients followed for what duration as well as consistent endpoints. He

also asked about the number of patients at Class III versus Class IV. Dr. Bourge said the randomized portion of the study was only the first six months, and after that physicians were able to use the hemodynamic data in managing both groups. He also noted that all patients who got the device were, and continue to be, followed. Dr. Somberg inquired why one year follow-up data was provided given there was no difference between the two groups at that time. Dr. Bourge said that data supports the application of the physiology and noted that benefit to the patient is an incentive for patients to enroll.

Dr. Normand asked if patients actually receive the data themselves. Dr. Bourge said the patient does not see the data. Dr. Normand asked why they chose to power the study to find a 30 percent absolute difference. Dr. Bourge noted there was no reference available in developing the protocol and that a composite endpoint was chosen so they could ensure they did not make patients worse. In calculating the power they assumed an event rate of 1.2 over six months, but the number of patient contacts lowered the event rate more than expected. Dr. Normand asked why they chose absolute versus relative and why 30 percent was clinically meaningful. Dr. Bourge said a 20 percent and a 30 percent difference is clinically important, and he said he thought it should be relative. Mr. Manda said their assumption was for a 30 percent relative reduction in the event rate. Dr. Normand said the analysis looked at absolute difference, and Mr. Manda said they compared the average event rates of the two groups, but in the power calculations they assumed a 30 percent reduction of an average rate of 1.2.

Dr. Brinker asked about the days alive and days alive outside of hospital being basically the same. Dr. Bourge said that in both Class III and Class IV there were sicker patients considered to be outliers, and they tended to be in the device rather than control group, which could explain why there was no significant difference in either total or mean days. Dr. Brinker asked if some of those days in hospital in the device group were related to device complications. Dr. Bourge said the median time for resolution of such problems was only one day, so it would not have contributed a lot. Dr. Brinker then asked how many encounters resulting in treatment changes occurred by telephone versus in person. Dr. Bourge said the majority of hospitalizations or urgent care visits were initiated by the patient and that there was no difference between the Chronicle and control groups in that regard. Dr. Stevenson said they did not have the data but in every

other study about 75 percent of interventions were made by phone. Dr. Brinker asked if part of the difference could be that there were more signals to see the patient in the device group as opposed to simply calling the control patients every week. Dr. Stevenson said the patient contacts, both by telephone and in clinic, were equivalent between the two arms.

FDA PRESENTATION

Matthew Hillebrenner, MSE, Division of Cardiovascular Devices, Office of Device Evaluation, provided an introduction to the agency's review of the PMA and introduced the other FDA presenters.

George Koustenis, M.A., Division of Biostatistics, Office of Surveillance and Biometrics, discussed the clinical trial. While the pre-specified safety endpoints were met, the pre-specified primary effectiveness endpoint was not.

Randall Brockman, M.D., FACC, Division of Cardiovascular Devices, Office of Device Evaluation, discussed the clinical implications of the COMPASS-HF trial. The treatment effect appears to be an absolute reduction of 0.18 heart failure related hospital equivalents per patient per six months in the Chronicle group compared to the control group. He also noted the apparent trend toward increased heart failure related hospital equivalent events in the New York Heart Association (NYHA) Class IV patients in the Chronicle group compared to the control group.

Nilsa Loyo-Berrios, Ph.D., Epidemiology Branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, discussed the proposed post-approval study developed with the sponsor. One question about which the agency seeks the panel's advice is in regard to whether all-cause mortality or heart failure mortality is a more appropriate outcome for use in the survival analysis. Another issue is the possibility of addressing possible rare adverse events post-market.

Dr. Maisel asked for clarification of Dr. Brockman's conclusion that there is a treatment difference based on NYHA classification given that fewer than 20 percent of patients were in Class IV and that the p-value was not significant. Dr. Brockman said the NYHA class was one of five pre-specified subgroup analyses and that in the Class IV subgroup the treatment effect appears to go in the opposite direction from the overall and the Class III.

Dr. Teerlink asked about Dr. Brockman's statement of there being 0.55 heart failure related hospital equivalents per patient per six months, and Dr. Brockman said it should have been per six months rather than per patient per six months.

Dr. Normand asked whether the last row on slide 54 refers to time to first heart failure related hospitalization rather than time to first hospitalization. She also asked for clarification of slide 55 whether events were assessed differently in the first six months compared to the last six months, and Dr. Brockman said his understanding was that all the events in this analysis were investigator adjudicated. Dr. Normand also asked for clarification of the interpretation of slide 56 about 0.18 heart failure related hospitalizations as admissions avoided. She noted that it was not statistically significant and that the confidence interval would include the possibility of an increase in heart failure admissions. Dr. Brockman said it was simply an attempt to make the number more meaningful for clinicians and that he did not intend to imply statistical significance, and he acknowledged Dr. Normand's point regarding the confidence interval.

Dr. Blackstone stated that the mortality statistics from after the crossover at six months are irrelevant and should be ignored. He also noted that on slide 47 only the Poisson or negative binomial models seem to have been considered although it is not a constant hazard. He suggested a Cox proportional hazard might get around that problem but wondered if the analysis was using the right distribution of events given that the hazard function is not constant. Mr. Koustenis said that based on earlier analyses and modeling the sponsor felt it was a reasonable approach and FDA agreed.

Dr. Somberg asked if they had looked at what happens to the differences based on NYHA classification after six months. Dr. Brockman did not think so. Dr. Somberg said that if the difference was due to the algorithm harming Class IV patients while benefiting Class III patients, then the difference should continue after six months.

Dr. Teerlink said in regards to slide 55 that it is possible that there were fewer investigator reported heart failure events because clinicians who have hemodynamic data think they can determine when a patient is being admitted for heart failure better. He cautioned against any interpretation implying durability of effect. Dr. Brockman noted it was not the primary effectiveness endpoint and that it was heart failure

hospitalizations not heart failure related hospital equivalents. Dr. Teerlink said his point was that the investigators were entirely unblinded as opposed to the primary endpoint where a blinded adjudication committee made the determination.

Dr. Hauptman asked about non-heart failure cardiovascular hospitalizations. Dr. Maisel suggested the sponsor could prepare an answer for later in the day.

PRIMARY REVIEWS

Dr. Borer noted that although adverse event rates were low, there was relatively small exposure and short duration of follow-up. He said the pre-specified primary hypothesis was not statistically supported by the data perhaps due in part to a lower than expected event rate in the control group, but also perhaps due to inherent deficiencies of the approach. Dr. Borer pointed out that the algorithm correctly predicted events about 75 percent of the time, which, while not perfect, may be better than other options. He also noted that since continual hemodynamic monitoring over many months has not been available before, the optimal medical response to the data provided by the device is unknown. Although the sponsor presented data to show that diuretics were not overused in the IHM group, given the sample size, few events, and possible marked individual variation in response to drugs, that analysis is not necessarily dispositive. Dr. Borer said it is noteworthy that when the blind was broken the event rate for the control patients fell to the value that continued in the IHM patients. Dr. Borer said his intuition is that the device is probably helpful, but questions remain.

Dr. Teerlink said the possible risks of the device are harmful changes in therapy, device related complications, the cost of the lost real estate on the patient's chest in terms of the future use of implantable devices, and the inability to undergo MRIs. Although in some early studies in the presence of dobutamine the relationship between dP/dt estimated PAD and the actual measured PAD was not consistent, they seemed to correlate well. Dr. Teerlink also highlighted that the 95 percent confidence interval for the 21 percent reduction in hospitalizations includes a 25 percent increase in hospitalizations. There was no pre-specified plan for analysis of secondary endpoints, none of which showed a significant difference. The durability analysis was confounded by investigator bias and unblinding. With frequent adjustments to diuretics,

patients are asked to do a lot in the absence of evidence of reduction in hospitalizations. Dr. Teerlink also emphasized the importance of the hospitalization required for the implant procedure and of device related complications and related rehospitalizations. He stated his belief that the data does not provide reasonable assurance of safety and effectiveness.

PANEL DELIBERATIONS

Dr. Domanski asked why the management of patients using data from the device at times failed to prevent a hospitalization. Dr. Stevenson said an early warning system will never be perfect and noted that the hospitalizations occurred in the Chronicle group following much quicker rises in pressure. She also pointed out the pressure elevations at the time of an event were less severe than in the control group.

Dr. Hauptman noted the reasoning is that following determination of optivolemia, which presupposes that the clinician can tell noninvasively when the patient is in reasonable clinical condition, the clinician needs to use the device to determine the condition of the patient. He also asked about concerns regarding the overuse of diuretics. Finally, Dr. Hauptman asked if it is possible the results from ESCAPE and COMPASS overlap. Dr. Stevenson said that there was not a lot of variation in patients' optimal estimated PAD and was pretty much what one would expect. Regarding the second question, she said that there is no evidence that IHM patients ended up using more diuretics on a chronic basis and that most interventions were one-time changes to diuretics. Dr. Hauptman wondered about overall exposure during the six months, and he asked about patients' beginning and ending doses. Dr. Stevenson said her impression is that maintenance doses did not really change over the six month period. She interpreted the results of the ESCAPE trial to suggest that monitoring the patients during hospitalization did not have much long term effect once patients return home.

Dr. Kato asked if they had considered using the device as an early warning system for the patients rather than their doctor. He also suggested that patients could simply pay attention to their salt intake and increase their dose without an expensive device. **William T. Abraham, M.D., Davis Heart and Lung Research Institute**, said it was an intriguing possibility but they felt in the initial studies a physician should be in charge of prescribing therapy. He envisioned a partnership between patients and caregivers and

suggested that it may be possible for patients to have better quality of life by eating what they want and then taking extra diuretic.

Dr. Normand said the unit of analysis should really be the physician and said the practical generalizations from the study are questionable because the physicians were not randomly selected. Dr. Stevenson said that the data is generally reviewed by health care professionals other than doctors, and when an alteration is detected it is efficiently reviewed by the physician and the health care professional makes the intervention. Dr. Normand asked if the same nurses were monitoring both the control and Chronicle patients, and Dr. Stevenson said yes.

Dr. Brinker said that although it was stated that patients with pulmonary hypertension due to non-cardiac causes probably should not be enrolled in this type of observational care, around half of the patients had some sort of pulmonary disease and almost half had sleep disorder. He asked if there were problems dissociating elevations in e-PAD between primary lung and primary heart. Dr. Bourge did not think the rate of lung disease was that high, and he said they tried to exclude patients with significant pulmonary disease. He emphasized that they are looking at trends over time and have learned to interpret them for individual patients. An ongoing sub-study is looking at diagnosing sleep apnea with the device. Dr. Brinker said they might see elevations in patients with heart failure who are ambulatory and mobilize fluid at night, and he asked how they distinguish that. Dr. Bourge said they look at nightly minimums when patients are not moving and that there is an activity sensor. They have seen patients with marked rises in nighttime pressure with volume overload, but BNP remained stable.

Dr. Somberg emphasized the critical role of a detailed therapeutic algorithm and said the device is an information source which will be used by a wide spectrum of people. He said the pressure assessment is used as a surrogate for end-diastolic volume and wondered if end-diastolic volume would be dissociated from the surrogate if patients not on beta blockers were given more intimate and inotropic therapy. Dr. Stevenson said they do not make calculations on volume but simple saying that when pressure goes up the most common reason is an increase in overall circulating volume. She said the association is very consistent regardless of the intervention and that they are not really measuring a surrogate for anything. Overall cardiac

volume may be changing, but circulating volume seems reliably associated with the pressure measurements regardless.

Dr. Ewald noted that even in the study's carefully selected, involved group of physicians and nurses the number of reviews of the data fell from 5.7 to 2.2 and wondered what would happen in the general heart failure population. Dr. Abraham said the patient population if approved would be similar to that studied in COMPASS-HF and that the plan is to initially roll it out the additional heart failure centers which can then help roll it out to the general cardiology community. Dr. Stevenson noted a revolution in quality of care is underway and that the current recommendation for all patients with advanced heart failure is to be followed in a heart failure management program which requires the kind of infrastructure being discussed.

Dr. Domanski asked the sponsor to explain how the trial demonstrates the effectiveness of the device in reducing hospitalizations. He also wondered whether the right patient population to study may have been those who have been in and out of the hospital. Dr. Abraham said they have demonstrated that one can use the data to treat elevated or depressed filling pressures including the data showing that clinicians respond appropriately to the data provided, and he also mentioned the biological plausibility as further support. He said there were a small number of outliers who in retrospect perhaps are not good candidates for the approach. Dr. Abraham also noted that a class IV Chronic patient was given an LVAD and subsequently had to remain hospitalized for 124 days because of the LVAD.

Dr. Page asked whether the device was put on the same side as a pacemaker in patients with a pacemaker and what kind of potential interaction between the two devices could be anticipated, and how that would apply to patients with non-Medtronic devices. Dr. Love said 53 percent of the patients at some point had a concomitant device, and there were no interaction issues. In general the devices were not on the same side. There were two patients with both on the same side, and there were no problems communicating independently with them. Though they did not look at having a device from a different manufacturer in this context, Medtronic has in the past, and no issues arose. He said chest real-estate is not an issue because leads can be extracted and new ones put in their place. Dr. Page said there would be an issue if there were an infection involving both shoulders, and Dr. Love agreed. Dr. Love said a study is underway looking at the

Chronicle ICD which combines the diagnostic and therapeutic operations of pacing, defibrillation, and hemodynamic monitoring. Dr. Page asked about the expected number of patients who would be candidates for the device if approved. Dr. Stevenson said the low EF and preserved EF populations would be the target and estimated somewhere in the range of 400,000. She emphasized that the device should be part of an appropriate heart failure management program and that perhaps only five percent of that number are currently managed under such a program.

Dr. Blackstone asked about a formal repeatable protocol for looking at the data. Dr. Adamson said there is a learning curve but once one becomes accustomed it is much easier to recognize changes outside the optivolemic range. A computer-based algorithm analyzes changes over time by looking at variability, duration, and magnitude of changes. Only 18 percent of events occurred without a prior detectable change in pressure. Dr. Stevenson pointed out that in the Chronicle group changes to diuretics brought about an appropriate change in pressures, but in the control group diuretics may have been changed too much or too little. Dr. Blackstone acknowledged there is evidence to support the post-hoc analyses conducted because of imbalances of some strong predictors of outcome but wondered why things like propensity scores were not used to adjust for those imbalances. He also asked why they only looked the first heart failure event. Dr. Bourge said there was a difference in six-minute walk tests in Class IV patients in the Chronicle and control groups and creatinine was higher in the Chronicle group. The multi-variable analysis showed that if one adjusts for baseline characteristics, there was a difference and the p-value improves to 0.11.

Dr. Somberg asked if the differences by class persisted in the six to twelve month period. Dr. Bourge said that after six months, events were investigator-adjudicated and that the correlation between investigator-adjudicated events and those adjudicated by the Clinical Events Committee (CEC) was over 90 percent. He said in class III patients the control group event rate fell to something similar to the overall Chronicle rate after six months and there was no increase of events in class IV patients. Dr. Somberg pointed out the possible role of bias in that analysis. Mr. Manda noted that only 28 of the 40 class IV patients made it to second six-month period and clarified there was over 95 percent concordance between investigator and CEC adjudication. Dr. Somberg said it is possible patients did not make it to second six-month period because of

a deleterious intervention resulting from the hemodynamic data. Dr. Maisel asked what had happened to the six class IV patients in the device group who were not included in the analysis. Mr. Manda said 12 class IV patients in the study died, eight being from the device group. Dr. Stevenson said the only thing which may have harmed patients would have been over-diuresing them, and she showed that there was no increase in events that could have been attributed to over-diuresis.

Dr. Somberg noted that for a drug two pivotal randomized controlled trials are required and wondered why the sponsor did not do more than randomized trial or one large one. Dr. Abraham said they felt at the outset that the study was adequately powered based on the assumptions presented earlier. Dr. Zuckerman said there is no requirement for two trials nor for a set sample size; rather, a trial should be powered to answer the appropriate questions.

Dr. Kato assumed the market would be larger than 400,000, and he wondered if there would be any attempt to improve battery life so the device would not have to be changed out every three and a half years. Dr. Steinhaus said they expect significant improvements to the device over time and pointed out that continual monitoring requires more energy. Dr. Kato then asked for more information on inclusion and exclusion criteria that will define a tight group of patients that will benefit. Dr. Steinhaus said they hope to learn more and hone down which patients will truly benefit when the device is rolled out to high-volume heart failure centers. Dr. Kato asked the FDA about funding for post-market surveillance and assurances that a post-approval study would actually be done. Dr. Zuckerman said the importance of following chronic device implants through the entire product life cycle has become obvious to all stakeholders and pointed to the role of post-market surveillance in the area of drug-eluting stents. He said there has been a fundamental shift over the past few years and believes there would be a genuine commitment to whatever the panel recommends.

Dr. Normand asked about the rationale for only including heart failure-related hospitalizations. Dr. Abraham said events were adjudicated by the CEC without reference to the hemodynamic data. He said they could not realistically expect the device to reduce events related to non-cardiovascular causes of hospitalization. Dr. Normand clarified that the data may have led to hospitalizations which turned out not to

be related to heart failure. Dr. Abraham showed that there was no increase in non-cardiovascular hospital equivalents. Dr. Normand asked the FDA about the trial design and the fact that they endpoint did not look at how the information is utilized. Dr. Zuckerman said the discussion should center on the trial completed by the sponsor and suggested that the heart failure experts on the panel could comment on her suggestion of an alternative means of looking at clinical utility.

Dr. Ewald asked if there had been any lead failures in the totality of the follow-up since the modification to the lead was made. **Jack Germanson, Medtronic**, said there were no failures in over 300 patients and more than 4,000 months of experience. Dr. Ewald inquired about the fact that there no ER visits or urgent visits to clinic among the class IV patients. Dr. Bourge noted that if a patient came to the emergency room and was admitted, it counted as a hospitalization rather than an emergency department visit. Noting the importance of looking at long-term trends in the data and that the number of reviews decreased from 5.7 to 2.2 times a month, Dr. Ewald asked if the effectiveness would be hampered if the data is only looked at once or twice a month. **Michael Zile, M.D., Medical University of South Carolina**, noted that the trends go up over a period of more than two weeks starting well in advance of symptoms sufficient to require hospitalization and that it was only patient contacts decreased. The data continued to be transmitted once a week. Dr. Zile said the utility of the device is what enabled the clinicians to only call patients when necessary. Dr. Somberg noted that diastolic pressures increased in less than seven days. Dr. Zile agreed that it is possible that selected patients may be selected for more frequent downloads and individualized care.

Dr. Brinker asked about the availability and potential use of temperature and heart rate data provided by the device and whether there was a way to alert physicians when something abnormal is found. Dr. Adamson said they are developing triggers and notifications and that later iterations may include heart rate variability and other derived measurements. Dr. Steinhaus said temperature is included as a pressure measurement and said that occasionally things like pneumonia have been identified using temperature. Noting that nearly half the medication changes during the randomized period were non-diuretic, Dr. Brinker asked about the undefined cardiovascular drugs it was used for. Dr. Stevenson said volume status dictates adjustments to a number of other medications, including potassium supplementation.

Dr. Hauptman asked how a lead revision was classified and whether any patients crossed over to other device technologies. Dr. Abraham said the events which comprised the primary endpoint did not include rehospitalizations for device-related events. He said a small number of concomitant devices were implanted after enrollment in the trial. Dr. Hauptman then asked for data on the time from a phone call in either group to a subsequent admission or event. Dr. Stevenson said they did not have that information but pointed out that the majority of events in both groups were initiated by the patient, not the clinician. Dr. Hauptman suggested that the device should not be used in patients with new onset heart failure which may resolve and also that the post-approval study should look at results of the device in centers that do not have prior experience from clinical trials. Dr. Steinhaus said they are open to changes in the design. Dr. Blackstone said such a design would be permanently confounded by institutional factors and propensity scores would not help.

Dr. Fleming asked about the possibility of combining the device with an infusion pump so the patient could avoid having to go the hospital as much and for a summary of the benefits to patients. Dr. Steinhaus said there could be enormous advantage in the ability to manage patients using such devices. Dr. Stevenson talked about the reassurance that patients can get that they are okay simply by transmitting their data.

Dr. Yaross said that interaction with the physician is a factor with many medical devices and suggested that sponsors should not be penalized for random, unlucky occurrences.

Dr. Maisel asked about patients where there was a significant difference between the actual value from the PA catheter and the estimated pulmonary artery diastolic pressure from the device. Dr. Adamson mentioned the vagaries regarding transmission of pressure in a fluid-filled catheter system compared to an instantaneous sensor and said there was much better correlation in the early ePAD studies which used high-fidelity Malar catheters. Dr. Maisel asked for a biological explanation of the differences related to New York Heart Association classification and wondered whether the device should be explanted when a class III patient becomes a class IV. Dr. Abraham was reluctant to draw any real conclusions given the size of the class IV subpopulation. He mentioned the possibility that some patients were diuretic-resistant. Addressing

the biologic plausibility of improvement in class III patients, Dr. Stevenson provided data showing that pressures declined over time in the Chronicle group and in the control group after it was unblended.

Dr. Maisel asked the sponsor which specific leads it was seeking approval for. Mr. Manda said both 4328(a) and 4328(b). Dr. Maisel asked which had the problem with the hermetic seal, and Mr. Manda said it was (a) but that the manufacturing correction was made prior to the start of COMPASS-HF. He said they are essentially the same lead. Dr. Maisel pointed out that 29 hospitalizations could be avoided by 124 implants, which themselves require hospitalizations.

FDA QUESTIONS

1. Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the entire study population.

2. (a) Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the NYHA class III patient population alone.

(b) Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the NYHA class IV patient population alone.

Dr. Teerlink said he sees no evidence that the device reduces patient hospitalizations for worsening heart failure. The panel felt the primary effectiveness endpoint was not met. Many, but not all, members felt the device is effective at measuring pressures and felt intuitively that the approach probably works. Regarding question two, most felt it is inappropriate to do subgroup analysis of the unmet primary effectiveness endpoint and that there was not enough data.

Dr. Zuckerman asked about the argument that frequent communication with the control group led to outstanding care which affected the primary endpoint calculation. Dr. Borer said the outstanding care provided to the controls should be the standard of care. Dr. Teerlink suggested a third arm with a more typical level of care would have been helpful.

3. Please provide your clinical and/or statistical interpretation of the secondary endpoint results for the COMPASS-HF study.

Members felt the secondary endpoints did not reach significance, and only some pointed in the right direction. One member suggested that mortality should be an additional secondary, rather than primary, endpoint in any future study. Another member suggested looking at patients' overall well-being in future studies. One member said that randomization should have taken care of baseline differences and that if one adjusts by covariates, it must be on the same scale as the observations.

4. Please provide your clinical and/or statistical interpretation of the results of the primary safety endpoint analyses.

One member said that although the sponsor met the arbitrary pre-specified safety criteria and did not feel that the risks had been completely defined. Dr. Brockman said the sponsor's safety endpoints are frequently used in implantable device trials. One member felt the endpoints would have been reasonable if the results were outstanding and was concerned that dislodgement and entrapment occurred even with the stellar team of implanters used in the trial and with the issue of repeated change-outs.

Dr. Teerlink noted that his analysis was flawed and the actual rate of device-related complications was around half of what he presented. Dr. Borer asked for clarification of the statement that precautionary measures should be taken prior to performing an ultrasound. Mr. Manda said the recommendation is simply not to place the ultrasound probe directly over the pressure sensing lead.

The panel in general felt the sponsor has demonstrated safety, but there are concerns about rare events and ongoing issues that would need to be evaluated in a post-approval study.

5. Please provide your clinical and/or statistical interpretation of the survival analyses discussed in the panel pack and presentations.

Dr. Blackstone said there were very few patients followed up at six months and that the Kaplan-Meier completion effect should be ignored. Dr. Maisel agreed that most of the panel feels that after the crossover there is little value in doing the analysis.

6. (a) Please discuss whether the proposed indications for use adequately define the patient population studied and for which the device will be marketed.

(b) Please discuss whether the labeling accurately informs patients of the risks of the device.

(c) Please discuss whether there are any other issues of safety or effectiveness not adequately covered in the labeling.

One member said the phrase about reducing hospitalizations should be omitted from the labeling. Another suggested “established heart failure of more than 6 or 12 months” rather than “moderate to advanced heart failure.” One member raised the issue of different standards of evidence required for drugs and devices making the same therapeutic claims. Another noted that the trial population was much younger than would typically be seen in practice and emphasized that the trial population should be described somewhere. A member suggested focusing on patients who require more than one hospitalization within the selected time period. Another suggested including a statement that the device be utilized in a heart failure management program.

7. Please comment on the adequacy of the training plan given the range of expertise of the physicians who may access the device and use the data in patient care.

Regarding specific implant training, one member said those who implant pacemakers have the technical expertise and that operator-to-operator educational materials would help avoid any pitfalls particular to this device. Dr. Maisel asked how many procedures might be required of a physician before she were read to implant the device without a proctor. Dr. Steinhaus suggested that five or ten procedures would be adequate for a physician used to implanting similar leads. A member said that a precise algorithm for interpreting and acting on the information could ensure effectiveness in the general population.

Dr. Zuckerman asked about training average physicians to use the technology well. Dr. Ewald proposed initially targeting centers used to caring for advanced stage heart failure patients. He was concerned about the risks of over-diuresis if there is simply a prescription for what to do in various scenarios. Dr. Zuckerman asked about training physicians and nurses in places where structured heart failure management programs are not available. Dr. Ewald emphasized explaining the features of the type of program that would really ensure the device remains effective.

A member said that you can’t teach people the best way to apply the information since that remains unknown. Another emphasized that simply implanting the device without then managing the condition using

the information exposes the patient to the risks of the procedure with no benefit. One member said the training should be a serial program involving at least two contacts with those providing the training.

8. Based on your review of the device, please comment as to the suitability of the proposed post-approval study, and, if applicable, please discuss any other elements that should be included in the post-approval study.

One member said they would need to enroll more patients to account for the fact that there will no longer be independent observation and suggested that successful use of the information might be a more appropriate endpoint than an impact on heart failure hospitalizations. Another said the proposed design would lead to a better point estimate of safety issues, suggested looking at refinement of the algorithm, which could also help assess whether inaccurate use of the data may cause any adverse events, and argued in favor of using all-cause mortality. Another member stressed the importance of peer-to-peer interaction among the multi-disciplinary team providing care.

Dr. Maisel said a registry could be used to assess rare adverse events and asked if a control group would be needed for the registry data. One member said that once the device is approved a control group presumably will not provide any new information, and another questioned whether it would even be ethical to have a non-device control at the point.

One member suggested using all-cause hospitalization and cardiovascular plus device-related mortality as the primary endpoint and did not think there would be a good control group. Another said that following approval mortality would be the critical issue, and a control group would be needed to demonstrate improved mortality; he suggested in that circumstance it would be entirely ethical to randomize patients. Dr. Maisel said only a randomized trial, not a post-approval study, would be able to definitively answer the mortality question. One member disagreed and said especially with devices a staged approach and aggressive post-approval studies are necessary. One member did not think it reasonable to require a very large post-approval study. One member suggested that some sort of imperfect control group would be better than none.

Dr. Zuckerman agreed with the necessity of a control group in post-market studies and asked Dr. Normand for practical suggestions. Dr. Normand doubted it would be the case that every single patient at sites where the technology was available would take it and said she would prefer to have a control confounded by site and team effects rather than no control. She suggested attempting to measure confounders a priori. She agreed with Dr. Maisel that it would be helpful to begin soon, before the device becomes available, collecting data on patients.

9. Provide your overall assessment of the risks and benefits of the Chronicle Implantable Hemodynamic Monitor as demonstrated in the pre-market approval application.

Dr. Maisel said members would be asked to answer this question individually following the vote.

SECOND OPEN PUBLIC HEARING

No members of the public asked to speak.

FDA AND SPONSOR SUMMATIONS

The FDA had no further comments.

Dr. Steinhaus acknowledged the difficulty in being asked to approve something which did not meet its primary endpoint. He said this is a new paradigm and the endpoints are not entirely clear and suggested that getting the device into the hands of physicians is one way of learning more about it. He said they have demonstrated that the measurements are accurate, reliable, and stable. He suggested that Swan-Ganz catheters are no longer the gold standard and that this device is the new standard and said that no one had done a study demonstrating improved outcomes with the use of Swan-Ganz catheters. Dr. Steinhaus said the sponsor has demonstrated that the pressures being measured relate directly to events and to symptoms and that the device is safe. He urged the panel to consider some sort of approval, even if it required a labeling change.

Dr. Stevenson said the sponsor had satisfied the FDA some years ago regarding diagnostic accuracy of the device. She acknowledged that the algorithm can be further refined, and she pointed out there is no signal that patients are being over-treated. She said they want the device to be approved as a diagnostic, not therapeutic, device for monitoring filling pressures in the context of a heart failure management program.

Dr. Abraham acknowledged the enthusiasm of some stemming from the biologic plausibility of the approach. He said the selection of the primary endpoint had resulted in the discussion focusing on therapeutic rather than diagnostic implications. He asked whether outcomes are necessary for approval of a diagnostic device. Dr. Abraham stated that had they chosen heart failure hospitalizations, the most common measure of morbidity in heart failure clinical trials, rather than heart failure events, the outcome would have been positive. He noted there were no device-related deaths and no indication of adverse events related to over-diuresis.

PANEL VOTE

Dr. Domanski asked whether measuring pressures is an approvable indication. Dr. Maisel said it is within the panel's purview to change the intended use. Dr. Zuckerman said there must be demonstrated clinical utility for a positive vote.

Dr. Teerlink made a motion that the device is not approvable. Dr. Somberg seconded the motion.

Dr. Somberg said although he feels that the device may have utility, it has not been proven. Dr. Borer stated that a diagnostic test is appropriate for application only if it is known how to use it. Dr. Brinker suggested it should be approved with a very limited patient population. Dr. Page said it has not been demonstrated that there is a population that would benefit.

Dr. Maisel called the question. The motion carried by a vote of nine to two. Dr. Maisel asked each member to explain his or her vote.

Dr. Domanski said he was persuaded that it was not shown that the device is clinically efficacious.

Dr. Page agreed that it must be demonstrated to be effective prior to approval.

Dr. Blackstone agreed and felt the fundamental problem may have been the selection of endpoints.

Dr. Teerlink said there was nothing in the data to counterbalance the downsides of the implantation, initial hospitalization, and occasional rehospitalizations for device-related complications.

Dr. Somberg said appropriate randomized controlled trials are needed to provide data sufficient to approve the device.

Dr. Kato said he would have liked to have seen the evidence.

Dr. Normand voted yes due to the lack of demonstrated therapeutic efficacy given the safety issues.

Dr. Ewald said there was no clear-cut evidence of benefit to the patient.

Dr. Brinker said he voted no because he believes there could be a limited applicability which would not have dissuaded the sponsor from conducting appropriate trials for the broader clinical population. He said it is a diagnostic device which is as effective as invasive data.

Dr. Borer said he had not seen information on how to use the device to derive benefit for the patient. He also said the device must be held to current standards, not those of the past.

Dr. Hauptman voted no because he felt it was conceivable to construct restrictive labeling to allow the device into the market.

Dr. Fleming said he would have voted no because of the device's future potential and his belief that it could have been made available in some restricted manner.

Dr. Yaross noted that it is not necessarily the responsibility of a sponsor to determine the impact of every device on mortality.

Dr. Maisel then asked for comments on the least burdensome way for the sponsor to provide additional data to enable the panel to find the device approvable.

Dr. Somberg said they need additional data from a larger randomized clinical trial and that there are a lot of possibilities for endpoints. He suggested that improved mortality is what patients really want. Dr. Maisel asked about the possibility of continuing the protocol, enrolling more patients, getting penalized for interim analysis, and then meeting the primary endpoint. Dr. Somberg said that was a great possibility and would be supportive of such data.

Dr. Borer said that reducing hospitalizations is an adequate endpoint. He suggested choosing a sicker population to study, refining the endpoint, powering the trial better. He said that changes would have to be made rather than simply extending it.

Dr. Normand felt that an integral part of a diagnostic tool is how one uses the information, and suggested looking at things like clinician or research team variability. She said that if the endpoints remained the same, with the possible exception of adding in hospitalizations related to the implant itself, the sponsor

could simply accrue more patients, taking into account the clustering issues, but that it would be difficult to penalize appropriately. She also returned to the issue of clustering.

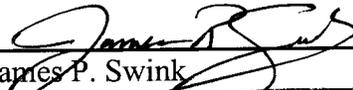
Dr. Domanski said hospitalization is a reasonable soft yet appropriate endpoint. He said the trial was under powered. He said he is actually somewhat bothered by how negative it was and wondered if there might actually be something wrong with the paradigm.

Dr. Maisel said a more specific patient population might help increase the treatment effects. He did not have a problem with the endpoint and said that more patients are needed. Dr. Borer agreed that heart failure hospitalizations is a perfectly adequate endpoint but noted that the sponsor used hospital equivalents.

ADJOURNMENT

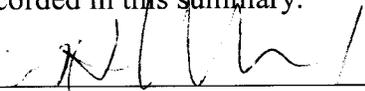
Dr. Maisel adjourned the meeting at 4:59 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on March 1, 2007, and that these minutes accurately reflect what transpired.



James P. Swink
Executive Secretary

I approve the minutes of the March 1, 2007, meeting as recorded in this summary.



William H. Maisel, M.D., M.P.H.
Chairperson

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