SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

October 27, 2020

VIA VIDEOCONFERENCE

Attendees:

Chairperson

Richard A. Lange, M.D., MBA
Texas Tech University Health Sciences Center El Paso
El Paso, Texas

Voting Members

George W. Vetrovec, M.D., MACC, MSCAI
Pauley Heart Center
Richmond, VA

Randall C. Starling, M.D., M.P.H.
Kaufman Center for Heart Failure Cleveland Clinic Cleveland, OH

Jason T. Connor, Ph.D.
ConfluenceStat, LLC
Orlando, FL

Ralph G. Brindis, M.D., M.P.H., MACC, FSCAI
University of California, San Francisco
San Francisco, CA

Temporary Voting Members

Janet Wittes, Ph.D.
Statistics Collaborative, Inc.
Washington, D.C.

Pramod Bonde, M.D.
Yale School of Medicine
Woodbridge, CT

Richard Page, M.D.
The University of Vermont Medical Center
South Burlington, VT

David Yuh, M.D.
Stamford Health
Stamford, CT

Robert W. Yeh, M.D., M.Sc, M.B.A.
Harvard Medical School
Boston, Massachusetts

Keith B. Allen, M.D.
MidAmerica Heart Institute
Kansas City, MO

Wayne Batchelor, M.D.
Inova Heart & Vascular Institute
Fairfax, VA

Erik Magnus Ohman, M.D., FACC
Duke University
Durham, NC

Joaquin E. Cigarroa, M.D.
Oregon Health & Science University
Portland, OR

John Hirshfeld, M.D.
University of Pennsylvania School of Medicine
Philadelphia, PA

Verghese Mathew, M.D., FACC
Loyola University Medical Center
Chicago, IL

Bernard Gersh, M.D.
Mayo Clinic College of Medicine
Rochester, Minnesota

John Somberg, M.D.
Rush University
Lake Bluff, IL

Jeffrey Borer, M.D.
SUNY Downstate Health Sciences University
Brooklyn, NY

Consumer Representative

Jacqueline Alikhaani
American Heart Association
North Hills, CA

Patient Representative

Debra Dunn
Heart Patient
Libertyville, IL

Designated Federal Officer

Aden Asefa, M.P.H.
Food and Drug Administration
Silver Spring, MD

CALL TO ORDER

Panel Chairperson Richard A. Lange, M.D., MBA, called the meeting to order at 9:00 a.m. He noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. He announced that the Panel would be discussing, making recommendations, and voting on information related to the premarket application for the Neovasc Reducer System.

PANEL INTRODUCTIONS

Chairperson Lange asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT

Aden Asefa, M.P.H., Designated Federal Officer, read the Conflict of Interest statement and reported that no conflict of interest waivers had been issued.

She announced that Gary Jarvis would be serving as the Industry Representative.

TEMPORARY VOTING MEMBER STATUS STATEMENT

Ms. Asefa read the Appointment to Temporary Voting Member Status Statement and appointed Drs. Wayne Batchelor, Pramod Bonde, Jeffrey Borer, Joaquin Cigarroa, Bernard Gersh, John Hirshfeld, Verghese Mathew, Erik Magnus Ohman, Richard Page, John Somberg, George Vetrovec, Janet Wittes, and David Yuh as temporary voting members.

GENERAL ANNOUNCEMENTS

Ms. Asefa then made general announcements to the public regarding transcripts and introduced Lindsey O' Keefe as the FDA press contact.

SPONSOR PRESENTATION

Vicki Bebeau, Vice President of Clinical and Regulatory Affairs at Neovasc, informed the Panel that the sponsor would be presenting data on the Reducer device for patients who, despite receiving optimal medical treatment, continue to suffer from refractory angina pectoris. She stated that the sponsor believes the Reducer has a favorable benefit-risk profile for the following reasons:

1. The primary endpoint for effectiveness was met.
2. A safe use profile has been established.
3. The device is intended to treat a "no option" patient population with a very poor quality of life.

She noted that the Reducer matches the description of Example 1(a) in FDA's published guidance on considerations of uncertainty in determining benefit-risk, in that it

also is a breakthrough device intended to treat a treatment-resistant condition. She further noted that this example incorporates a discussion of three scenarios of ambiguity and concludes that higher levels of uncertainty create increased reliance on postmarket data collection.

She announced that the company has proposed a robust postmarket study that is consistent with FDA's regulatory strategy on harmonizing pre- and postmarket data accumulation for devices that are subject to premarket approval.

She then outlined the agenda for the remainder of the presentation.

Timothy D. Henry, M.D., focused his discussion on refractory angina, key aspects of the patient population, and the unmet clinical need. He noted that these patients are a very specific subset with lack of capacity and high healthcare utilization, that they currently have very few treatment options in the United States, and that they are a very challenging patient population to treat.

Shmuel Banai, M.D., discussed the mechanism of action. He explained that the Reducer restores the endocardial to epicardial blood flow ratio to normal by increasing coronary sinus pressure; that it improves blood flow to the ischemic subendocardium, increasing left ventricular contractility; and that it reduces left ventricular end-diastolic pressure.

Victoria Hampshire, V.M.D., presented the following findings from preclinical animal data:

- There was adequate localized tissue-connecting gross pathology and histology with an absence of migration and perforation.
- There was a 100% coronary sinus lumen endothelialization and tissue proliferation at proximal and distal ends of the Reducer.
- There was incomplete coverage of the midsection struts and preservation of lumen from proximal to distal.
- This includes luminal preservation through the midsection with low levels of inflammation at all time points and in all sections, and evidence of 10% stenosis at the mid-plane consistent with the intended effect of the Reducer geometry.

She noted that these findings support the mechanism of action.

Serge Rousselle, D.V.M., DACVP, provided details on Reducer midsection endothelialization. He informed the Panel that the sinus lumen tissue was fully endothelialized, as was the device wherever it made contact with the host tissue. He presented information on two cases, one being the most advanced tissue integration of the device and the other, the least advanced at mid-level. He noted that negative restenosis values presented in the pathology report resulted from an artifact of calculation.

Gregg W. Stone, M.D., FACC, FSCAI, reviewed the study design of the Reducer trials, summarized the COSIRA data, and presented safety and effectiveness outcomes. He reported that the sham-controlled COSIRA trial met its primary pre-specified powered

endpoint, noting that a two-class or greater improvement in CCS angina class from baseline to 6 months was present in 35% of Reducer patients versus 15% of sham-control patients. He further noted that the secondary non-powered endpoints were directionally supportive of the primary effectiveness results. He informed the Panel that there was more than a 50% reduction in the number of serious adverse events with the Reducer compared to no Reducer, and that the totality of the evidence in more than 2,000 distributed Reducer devices has demonstrated that it is safe when used as indicated.

Dr. Henry reviewed the clinical aspects and key points. He reiterated that refractory angina patients in the United States are desperately in need of new options, that the Reducer meets the criteria for safety and effectiveness, and that there has been significant improvement in symptoms and quality of life.

Q&A

Bram Zuckerman, M.D., identified slides from the sponsor's presentation containing data that were not reviewed by FDA. He instructed the sponsor to specify unapproved data, whether hypotheses were pre-determined, and if multiplicity adjustments were made.

John Somberg, M.D., asked if pharmacological therapy for angina was maximized during the 30-day sequential testing period; why a third of the patients were either not on antianginals or were on blood pressure medicines that were not antianginals; if the medicines remain constant; and if doses were maximized. He also requested an assessment of cardiac catheterization data.

Richard Page, M.D., inquired as to how the sponsor knows that the benefits are due to coronary sinus stenosis. He asked if the reverse hourglass shape of the stent in Animal 1111 on slide 45 was intentional and if the procedure requires two stenoses. He also asked for further comment on the physiology connected to the stent's effect on pressure in the coronary sinus.

David Yuh, M.D., asked if the exclusion of microvascular disease was partly responsible for the low number of women in the study. He also asked what the total procedural time difference was between the sham and treatment groups.

Keith B. Allen, M.D., asked if coronary surgeons were involved in the assessment of revascularization; how the effectiveness of blinding was confirmed; and who managed the post-op medications and changes in medications in both groups. He also asked if pressure measurements could be provided.

Joaquin E. Cigarroa, M.D., asked if the individuals who assessed angina were blinded to medications, including dual antiplatelet therapy; if there were any differences in the diastolic filling period between patients who responded and those who did not; and if measurements were taken across the stent at rest and during increased heart rate.

Janet Wittes, Ph.D., asked what countries enrolled the 104 patients; what percentage of them were current smokers; and if the patients in slides 75, 77, 78, and 81 represent the entire group at six months, one year, and two years. She also asked the sponsor to show the movement of Class III and IV patients in both groups.

Verghese Mathew, M.D., commented that 25% of patients on zero or one medication does not appear to be refractory and asked for an explanation. He then requested information on changes or adherence to medications during follow-up in the COSIRA and REDUCER

studies. He pointed out that the indications for use do not specifically exclude patients with microvascular angina and suggested that the proposed IFU should read myocardial modification. He also asked the sponsor to expound on technical mishandling of the device in eight of the COSIRA patients.

Ralph G. Brindis, M.D., asked how the 2,000 follow-ups with no coronary sinus thrombosis was documented. He also asked for comment on the issues of scan evidence of thrombus within the device, and long-term antiplatelet therapy.

Jeffrey Borer, M.D., asked if the investigators who assessed limited options and outcomes were unblinded.

Jason T. Connor, Ph.D., asked for an explanation as to why the trial stopped short of planned enrollment. He also asked to see outcomes by site.

Robert W. Yeh, M.D., asked if the angiograms were reviewed by interventionalists or surgeons by current standards as opposed to those that existed at the time of the trial. He also asked why enrollment was limited to patients with ischemia attributable to the left coronary system.

Dr. Somberg asked why the sponsor decided to use aspirin instead of anticoagulants.

Wayne Batchelor, M.D., asked for a correction calculation of one hypothetically misclassified patient to see what the impact on statistical significance would be. He also asked if the device would preclude future coronary sinus intervention.

Randall C. Starling, M.D., acknowledged that "no option" patients do have the option of cardiac transplantation. He asked for comment on pressure measurements, coronary sinus oxygen content, and vascular resistance, as well as information pertaining to durability and movement of the patients. He also asked which patient populations with refractory angina will be suitable for this.

Bernard Gersh, M.D., questioned how 25% of patients on zero or one antianginal agent fits into the definition of refractory angina. He asked why the trial was terminated sooner than expected and why patients were so happy with their treatment since there was a considerable discrepancy in terms of angina relief. He also asked for data showing correlations between clinical results and mechanistic findings.

FDA PRESENTATION

Samuel Raben, Ph.D., outlined FDA's presentation. He discussed the regulatory history and considerations, gave a device description, and reviewed nonclinical evaluations conducted in support of the submission.

Annabelle Crusan, D.V.M., M.S., presented FDA's review of the sponsor's non-GLP porcine studies. She highlighted concerns regarding the overall quality and integrity of the study data, indicating that final reports were incomplete, that there was missing data, and that protocols could not be verified due to missing information and lack of amendment and deviation records. She noted that there was no confirmation of sufficient device coverage by neointima to restrict coronary sinus blood flow to the narrowed device central orifice, no validation of coronary sinus stenosis or elevated coronary sinus pressure, and limited evidence of improved myocardial contractility and blood flow.

Rong (Rona) Tang, Ph.D., assessed the study design, statistical method, and analysis

results of the COSIRA study. She reported that the primary effectiveness endpoint was met, that there is a high percentage of missing data, and that interpretation of the secondary endpoint analysis is challenging. She specified that the study does not have a primary safety endpoint, that there is no statistical hypothesis for secondary endpoints, and that the large number of secondary endpoints with no multiplicity adjustments creates the potential for false positive findings.

Tara A. Ryan, M.D., presented the COSIRA clinical study results. Topics covered included data collection, inclusion/exclusion criteria, and patient demographics. She noted that the study was not representative of the minority or female populations. She also discussed the limitations of the study, noting that there is substantial clinical evidence of a placebo effect, especially for the relief of pain. In addition, she pointed out that the study was not statistically powered to detect an improvement in ischemia by objective measures, that there was a significant amount of missing data for the secondary endpoints, and that long-term safety data is inadequate.

Dr. Raben recapped the presentation and discussed the proposed post-approval study. He informed the Panel that the sponsor is suggesting a randomized, double-blind, sham-controlled trial to be performed in a country where the Reducer device has not been approved. He noted that the intent of the study is to clarify major questions about the current clinical data, but implementation of the trial may be difficult.

Q&A

Dr. Cigarroa asked if the primary data for LV contractility and perfusion was reviewed. He also asked for FDA's perspective on the probability of Type 1 error and for information regarding diastolic function with coronary sinus pressure.

Dr. Somberg posed the following questions:

- Was there any missing CCS data?
- Did FDA conclude that this is not a refractory angina patient population?
- Is there a procedure in the COSIRA-II trial that would ensure that the patients are a "no option" population for both drugs and intervention?

George W. Vetrovec, M.D., asked if a clear understanding of the mechanism of action is a requirement for approval. **Dr. Zuckerman** replied that it is helpful when there is uncertainty regarding other variables, but it is not required.

Dr. Yuh asked what the expected placebo rate would be for this type of study.

Dr. Starling asked what the heart team was composed of and if there is information regarding anginal relief beyond the six-month primary endpoint.

Dr. Connor requested information regarding the natural variability of the regression to mean among these patients or history-of-life patients.

Erik Magnus Ohman, M.D., asked if FDA has looked at the discrepancy between the change in the Canadian classification and the SAQ frequency of angina questions.

Dr. Allen asked what the normal safety standard is that FDA would require for a

permanent intravascular device.

Dr. Wittes asked what aspects of the study were not approved by FDA and what was known when the trial was stopped prematurely.

Dr. Connor asked why there is missing data for the secondary endpoints.

John Hirshfeld, M.D., asked if the sponsor collected CT angiogram data on patients in the COSIRA study.

OPEN PUBLIC HEARING

Meg Seymour, Ph.D., spoke on behalf of the National Center for Health Research. She urged the Committee to require additional premarket data from a randomized, properly blinded, sham-controlled study with a representative patient population. She pointed out that this kind of information is needed to determine the effectiveness of the device and whether it is adequate for approval. She remarked that the evidence provided so far does not prove that the benefits outweigh the risks.

Amir Lerman, M.D., speaking on behalf of the Mayo Clinic, stressed the need for a new therapy for patients with intractable angina. He pointed out that current medical treatments are not designed for treating these patients, nor are there any guidelines. He stated that the coronary sinus reducer appears to be safe and easy to use. He related that his clinic recently requested IDE approval from FDA to use the device and that the study will be starting soon.

Gerald Koening, M.D., Ph.D., revealed that he is one of the few U.S. cardiologists who has used the Reducer on a compassionate use basis for two patients. He reported that these patients have had significant reduction in their angina classification category, as well as a considerable improvement in quality of life. He related that the procedure is low risk, that a minimal amount of training is needed, and that patient tolerance of the procedure is exceptional. He added that recovery is rapid with results becoming apparent within six weeks. He asserted that this technology will make a significant impact in the quality of life for many patients in the United States.

Ryan Gindi, M.D., recounted the experience of a patient who was implanted with a Reducer device through compassionate use approval. He reported that this patient, who once had chest pain while walking to the mailbox, improved to the point where, three months later, he could stroll around Washington D.C. and ride a bike for 35 miles with no symptoms..

Frederick Casciano, a patient of Dr. Koening, told the Panel that his life deteriorated after being diagnosed with angina. He related that he suffered from severe depression, anxiety, and inability to sleep. He further related that after being implanted with the Reducer, he is able to once again go for walks and do work around the house, that he went on a 35-mile bike ride, and that he is enjoying life anew.

Annette Casciano told the Panel that her husband was diagnosed with heart disease at the age of 38, that he has had several heart attacks, that he has undergone bypass surgery

and angioplasty, and that he began to suffer with chronic angina when he was 51. She related that since receiving the Reducer, his energy has improved, his depression has decreased, and he is able to do things without the constant reminder of his heart disease. She added that other people have noticed a big improvement in him and that she no longer worries about losing him on a daily basis.

Mark Soberano described how his life fell apart after cardiac arrest and stent placement. He related that he has continuous chest pain with any kind of activity and that he constantly needs nitroglycerin. He further related that he can no longer work and is on disability, and that he can't participate in family activities. He asked the Panel to remember that this treatment has the potential to give him back some quality of life.

Steven Summers spoke of his experience with heart attacks and angina. He told the Panel that he had to give up his pursuit of a master's degree and goal of becoming a full-time minister, and that he is currently on disability as the result of a mild stroke. He related that he received a Reducer in 2018 and that for the last year and a half he rarely has angina. He reported that on a recent weekend trip, he was able to walk, bike ride, and ride a horse with only one instance of needing nitroglycerin.

Donna Summers depicted the limiting impact that her husband's angina has had on their lives. She related that the Reducer has greatly improved their quality of life, that he can do daily work without chest pain, and that he can take walks with the dog, play with their grandchildren, and go on vacation.

Laurie Vandenbossche described what it's like to live with angina. She told the Panel that she had to take an early retirement, that she is afraid to commit to volunteer work, and that she struggles with anxiety and depression. She also said that she has become withdrawn and fearful, and that she is afraid to make travel plans because of the frequency of her hospitalizations. She expressed hope that the Reducer will bring relief from constant anxiety and restore normality to her life.

Donald Scott told the Panel that he is no longer able to do some of the most basic things that he has always done, that his wife now mows the lawn, and that he can barely go up or down a flight of steps without getting winded or having to take a break. He stated that he misses the quality of life that he used to have, and that he would love to be able to take care of his home and pick up his grandchildren without the fear of getting lightheaded or dizzy.

Tammy Hopkins detailed the limitations that angina has imposed on her. She related that she is always short of breath and that she never knows when the angina is going to attack or how long it will last. She further stated that regular breathing or walking is devastating because of the pain. She concluded that the Reducer could be a helpful option of providing better quality of life.

Clyde Hart told the Panel that he was given compassionate use approval for the Reducer but the procedure has been postponed because the training physician cannot come to

the United States because of the COVID pandemic. He indicated that his quality of life has lessened in the last three months, and that severe breathing issues are hindering his ability to get around. He requested help in getting the device approved and seeing that doctors are trained to do the procedure.

SPONSOR RESPONSE

Dr. Stone provided information regarding pharmacological maximization 30 days prior to the procedure, including stability data on medications post-randomization.

Dr. Banai addressed questions about mechanism of action with regard to the Beck operation, and narrowing in the coronary sinus.

Dr. Stone explained that patients were evaluated by general cardiologists, interventionalists, and surgeons for eligibility. He confirmed that there was no blinding questionnaire and that post-op evaluations and management were performed by blinded investigators.

Dr. Banai provided data on pressure measurements in animals.

Dr. Stone informed the Panel that severe coronary artery disease was a requirement for acceptance into the trial, that there was no core lab analysis or formal evaluation of the intensity of the disease, and that all investigators and personnel who saw patients during follow-up were blinded.

Dr. Banai presented data showing improvement in diastolic function at six months for severe Grade III and IV Reducer patients.

Chris Mullin, M.S., explained that the decision to end enrollment was based on logistical concerns and not on safety issues or crossing of the pre-specified boundary. He affirmed that the results would still be significant if enrollment had continued to the originally planned sample size.

Dr. Stone confirmed that there was no interaction between the number of baseline medications and the primary endpoint results, and that there have been no reported instances of coronary sinus thrombosis. He also informed the Panel that all patients received dual antiplatelet therapy, and that future leads can easily be placed in the coronary sinus through the Reducer.

Pramod Bonde, M.D., asked if any differences were observed in the function of right ventricle versus the left. He also asked how that would impact patients who have a single territory non-revascularizable disease.

Dr. Stone informed Dr. Ohman that there was consistency between the SAQ questionnaire of angina frequency and the response in Canadian classification improvement. He also reported that there was a statistically significant reduction in angina quality, as well as substantial differences in frequency and stability.

FDA RESPONSE

Dr. Ryan addressed Dr. Connor's question regarding historical evidence with respect to regression to the mean. She informed him that a literature search was done, specifically with respect to the placebo effect and angina. She noted that numerous studies have shown that the placebo effect can vary in targeted muscle reinnervation studies and that an upper or lower limit could not be provided. She also informed Dr. Wittes that the major concern about COSIRA was the use of a subjective rather than objective endpoint.

Dr. Stone noted that there was a relatively small percentage of missing SAQ data. He also provided summary statistics of the CTA findings.

Dr. Hirshfeld asked what the minimal lumen diameter in the neck of the device is as opposed to the proximal and distal ends. He also asked for a quantitative tabulation of flow around the neck.

FDA QUESTIONS

Dr. Raben read Question 1: Over 90% of COSIRA subjects were taking at least one antianginal medication (93.3%), and 36.5% were taking 3 or more at baseline. However, in a trial intended for a refractory angina population, ≤ 25% of subjects were only on zero or one antianginal medication. Additionally, at baseline, approximately 75% and 50% of subjects were taking beta blockers or calcium channel blockers, respectively. No justification was provided regarding the proportion of patients prescribed beta blockers, nitrates, and Ca+ blockers in a refractory angina population. Also, no information was provided about medication compliance, or whether patients were on therapeutic or maximally tolerated doses.

When determining an acceptable indication for use statement, FDA must consider if the data provided supports a reasonable assurance of safety and effectiveness for a defined patient population. Please discuss whether the COSIRA trial identified and enrolled a defined patient population with refractory angina (despite optimal medical therapy).

Dr. Batchelor emphasized the importance of addressing this issue in another study. He advised that any study going forward should identify what the definition for refractory angina is, who governs the medications, and what the escalation protocol is for optimizing medical therapy.

Dr. Somberg stated that it is critical to have a defined population consisting of patients who are resistant to medical therapy.

Dr. Brindis recommended documentation of dosages at baseline and follow-up.

Dr. Mathew acknowledged the difficulty in optimizing medical therapy in real life as well as in clinical trials and suggested that this study is not necessarily an exception in terms of therapeutic aggressiveness.

Dr. Cigarroa observed that these patients are not reflective of U.S. demographics. He pointed out that the percentage of individuals who were intolerant to medications challenges the ability to interpret the results.

Dr. Vetrovec remarked that the number of patients who were inadequately treated is exceptionally high. He stressed the importance of having a better balance of good medical therapy.

Dr. Yeh commented that the patient population may not be the one explicitly named, but it is still a clinically relevant group with severe symptomatic coronary disease.

Chairperson Lange summarized the Panel's response:

- The sponsor has identified people with severe angina, but there is insufficient evidence to determine whether or not they are actually refractory.
- Future studies need to address what is missing in the data.

- The sponsor will have to make a better effort to denote refractory angina as opposed to severe.

Dr. Gersh insisted that these are patients with severe angina and are not truly refractory. He acknowledged that they probably were not able to be revascularized and noted that formal heart teams were not in existence at the time.

Chairperson Lange noted that the Panel feels there is not enough information to determine whether these patients are truly refractory.

Dr. Raben read Question 2a: Although subjects were blinded to their treatment group, there was no assessment of blinding success, such as a questionnaire asking subjects to identify the study arm to which they believed they were assigned. Additionally, the rate of missing data for dobutamine stress echocardiography (DSE) at the 6-month follow up was notably higher in the control group, which may indicate problems with the blinding. A notable placebo effect was also observed in the COSIRA control group, which presents challenges for interpreting the data given the limited sample size.

Please discuss the robustness of the trial results given the lack of a blinding assessment throughout the course of the study and limited sample size.

Dr. Ohman pointed out that interpretation is difficult without objective evidence of ischemia.

Dr. Somberg stated that the blinding issue is one of the better aspects and that he is most concerned about the missing data.

Dr. Batchelor stressed the importance of ensuring that all source documentation is completely obscure in terms of treatment assignment.

Dr. Connor remarked that the sponsor appears to have made a good attempt at blinding. He added that the missing data is very problematic.

Dr. Brindis stated that the missing data is a significant problem because of the imbalance between the two groups, and that the disproportion in terms of ethnicity and gender is a huge step backwards.

Dr. Allen remarked that the imbalance and missing data is concerning because of the possibility that patients figured out what treatment they were getting.

Chairperson Lange summarized the Panel's response:

- The success of the blinding cannot be determined because there was no objective assessment of it.
- The missing data raises concern that patients and/or their physicians may have figured out which treatment they received.
- Having evidence of ischemia would have been essential in this trial.

Dr. Brindis mentioned the possibility of detecting the device in chest X-rays.

Dr. Starling reiterated that there are numerous safeguards that can be employed, such as having investigators sign documents to verify that they have not been unblinded to the treatment.

Dr. Gersh highlighted the importance of verification of blinding not only at the time of the procedure, but also during follow-up.

Dr. Raben read Question 2b: Given that some patients do not appear to receive any benefit from treatment (only 34.6 achieved a primary endpoint success of a change in CCS of 2 or more and 28.8 demonstrated no change in CCS from baseline), we would like the Panel to discuss whether patients who are more likely to receive a significant clinical benefit can be identified prior to implantation of the Reducer device.

Dr. Yuh remarked that uncertainty about the mechanism of action is a hindrance to the Panel's discussion.

Dr. Starling added that the answer is the Panel doesn't know.

Chairperson Lange asked if there are any Panel members who believe they know which patients would receive a significant clinical benefit. There was no response.

Dr. Somberg opined that the benefit of the device probably has something to do with its implantation in the coronary sinus. He suggested doing studies on the distribution of drainage compared to where ischemia originates to possibly identify patients who would benefit.

Dr. Page acknowledged that he does not have a good enough understanding of the nature of the patients and the mechanism of action to be able to say who will benefit.

Dr. Ohman agreed that it is unclear. He pointed out that the best therapeutic data is derived from patients who took the minimal amount of medication.

Dr. Borer suggested that quantitative assessment should be given greater emphasis in a new study design.

Chairperson Lange summarized the Panel's response:

- The Panel does not know who would benefit.
- Information that is lacking includes correlation of the mechanism with clinical benefit.
- Demographics and distribution of coronary anatomy is ill-defined.
- There is no quantitative data to ascertain which patients received benefit.

Dr. Raben read Question 3a: Please discuss and comment on the subjective assessment of angina (change in CCS grade) as a clinically meaningful correlate of ischemia to support a reasonable assurance of Reducer device effectiveness.

Dr. Borer stated that the best evidence would be quantitative assessment that includes an electrocardiographic measure of ischemia, as well as antianginal effect. He asserted that a reduction in CCS grade is not sufficient.

Chairperson Lange asked the Panel members to vote by a show of hands as to whether they would recommend using only the CCS grade change, and if they think it is a reasonable assurance of effectiveness.

The Panel voted unanimously that it is not a reasonable assurance and should not be the sole measure.

Dr. Yeh pointed out that the goal is the reduction of angina, not ischemia. He pointed out that these patients do not care about their objective measurement of ischemia, but do care about how they are feeling. He added that he is more concerned about the blinding issue and would be more comfortable if there had been perfect blinding.

Dr. Cigarroa stressed the importance of assessing ischemia in addition to angina, especially with a small sample size.

Dr. Mathew agreed that patients are more concerned about having their symptoms reduced. He remarked that not having an objective measure of ischemia is discomforting.

Dr. Borer stated that he is also more concerned about the blinding issue. He emphasized the importance of having some assessment of ischemia.

Dr. Somberg suggested some means of verification that the device is more than a pain reliever and that it actually does alleviate ischemia.

Dr. Gersh agreed that both measurements are needed.

Chairperson Lange summarized the Panel's response:

- CCS alone is not an effective way to reasonably assure effectiveness
- Measurement of both angina and ischemia is recommended.

Dr. Allen stressed the relevance of allowing the mechanism to play a role in judging the primary endpoint. He observed that in this instance, CCS class is not the right endpoint.

Dr. Starling pointed out that the Panel was never told what the rigor was concerning the blinded assessment and agreed that something more than CCS is needed.

Dr. Raben read Question 3b: Please discuss and comment on the overall primary effectiveness rate of 34.6%, given the permanent implant nature of this device and vulnerability of this no-option patient population.

Dr. Allen stated that the number is acceptable, but the way in which the trial was done causes him to question if it was actually achieved.

Dr. Batchelor commented that the response rate is fairly good if the patient population is accurately defined. He added that the confidence intervals around the reduction is questionable.

Dr. Cigarroa stated that it is reasonable, but the issues with the trial cause him to doubt whether he believes it.

Dr. Somberg remarked that the number is very marginal.

Chairperson Lange summarized the Panel's response:

- Some Panel members feel that the rate is satisfactory and others do not.
- There is less concern about the number than there is about the reliability of the patient population and the assessment.

Dr. Raben read Question 4a: In a secondary effectiveness analysis in COSIRA, ETTs (bicycle ergometry and dobutamine stress echocardiography) were used to objectively assess ischemia. Subjects in the Reducer group had numerically longer exercise durations (mean increase of 64.7 seconds vs. a mean increase of 4.3 seconds) and time to ST-segment depression vs. control patients (76.3 seconds vs. 33.8). However, the study was (1) underpowered to detect an improvement in functional ischemia between treatment groups, and (2) there was a substantial amount of missing information. For DSE data, missing data was noted in roughly 15% of Reducer subjects, while about 30% was missing for the control subjects. Total exercise duration testing was missing in about 25% of all patients, and ST depression data was missing from 70-88% of patients. These two factors impact the conclusions that may be drawn from these ischemia data.

Please discuss overall Reducer device effectiveness observed in the COSIRA trial, considering the small sample size (underpowered study for ischemia endpoints), high control group response rate, significant amounts of missing data for objective ischemia assessments, and lack of pre-specified hypotheses tests for objective ischemia assessments.

Dr. Gersh commented that it is an underpowered study and he does not understand why it was stopped. He added that the lack of missing data and the discrepancy between the two groups invalidates the secondary endpoints.

Dr. Allen remarked that it is difficult for him to put much faith in the secondary effectiveness analysis. He observed that the sponsor did not do a pre-specified hypothesis and did not power the study for these endpoints, making it obvious that there was little confidence that they could be met.

Dr. Somberg commented that with that degree of missing data, the evidence presented will not be very informative.

Chairperson Lange noted that the study is underpowered, that there is missing data, and that it lacks a hypothesis for the secondary endpoints.

Dr. Zuckerman inferred that the nonrandomized REDUCER-I observational data was presented because the sponsor was partially aware of some of these problems. He asked Dr. Allen if he found that information to be helpful. **Dr. Allen** replied that it is not beneficial and that he disregards it. He further stated that merging randomized data from COSIRA with the REDUCER-I data only confuses the matter and draws into question many of the issues that were discussed.

Chairperson Lange noted that the Panel feels that the data from REDUCER-I does not overcome the shortcomings of the secondary effectiveness analysis.

Dr. Raben read Question 4b: Please also discuss if additional premarket objective ischemia assessment data are needed to support Reducer effectiveness (e.g., primary endpoint of the COSIRA-II trial: Change in total exercise duration in modified Bruce treadmill exercise tolerance testing at 6 months).

Dr. Somberg stated that COSIRA-II needs to define the population and then show that there is a reduction in angina related to ischemia.

Dr. Page asked for clarification as to whether the Panel is being asked if premarket objective assessment is needed or if it were done, if some objective evaluation would be required. He pointed out that the latter has already been answered and that the former cannot really be considered until the Panel discusses effectiveness.

Dr. Raben specified that it would be essential for the Agency to understand if the current totality of the data is sufficient or if additional data is needed to further support the proposed indication.

Chairperson Lange suggested that the Panel hold off on this question until it discusses effectiveness. **Drs. Zuckerman** and **Raben** concurred.

Chairperson Lange noted that due to technical difficulties, **Dr. Wittes** typed a response to the previous question. He then read it into the record:

- The fact that the secondaries are so weak and that there is so much missing data is troubling.
- The combination of a subjective primary outcome with non-convincing data on the secondaries makes the whole study uninterpretable coupled with the fact that this population is so unlike the U.S. population.
- There is too much missing data to be able to do any statistical fix.

Dr. Raben read Question 5a: As discussed in FDA's executive summary, there are limitations to the currently provided dataset. These limitations include, but are not limited to:

- Lack of a non-exercise primary effectiveness endpoint and no pre-specified hypothesis tests for objective secondary endpoints;
- Small sample size;
- Significant missing secondary endpoint information;
- Lack of a formal assessment for coronary sinus (CS) stenosis or severity;
- Lack of evidence of a CS pressure gradient across the device;
- High placebo response rate;
- Trial cohort demographics are not representative of the U.S. population.

In addition, the Reducer device is intended to create a CS stenosis resulting in a functionally significant increase in CS pressure gradient that may reduce myocardial ischemia by redistributing subepicardial blood flow to the subendocardium. However, in vivo animal studies were not sufficient to confirm tissue coverage to restrict CS blood flow to the Reducer's central orifice. Further, neither in vivo animal nor clinical data were provided to show that the Reducer device performed as intended because there were no adequate studies that assessed:

- The presence of severity of coronary sinus;
- A CS pressure gradient across the device; or
- The association of a CS stenosis or a CS pressure gradient with reduced angina or ischemia.

Please discuss and make recommendations whether additional pre-market data from a

randomized sham-controlled clinical study are needed to support the safety and effectiveness of the Neovasc Reducer System given the concerns and limitations with the currently available data.

Dr. Page stated that a new, correctly performed trial is clearly needed. He recommended that it be done in the U.S. and that it should provide objective as well as subjective measures of angina and ischemia.

Dr. Allen agreed. He remarked that it is odd that the proposed postmarket study is really what should have been the pivotal IDE trial, and that it would be unusual to do the preferred study after product approval.

Dr. Batchelor opined that most, if not all, of the Panel members feel that the current data is not good enough to provide any reliable answers in terms of effectiveness. He recommended a new, properly designed trial in the U.S. with adequate site selection that would better represent the demographics. He asked if Dr. Allen's observations are derived from the breakthrough designation.

Dr. Zuckerman explained that the issue centers mostly on a disagreement between the sponsor and FDA on current implications that provide flexibility in dealing with uncertainties, when appropriate, in the postmarket phase. He specified that this is what the sponsor wants to do, whereas FDA believes that these particular uncertainties would be better addressed in a premarket randomized trial.

Dr. Mathew stated that he believes the Panel would like to see the pivotal trial. He pointed out that there are other pathways that could be taken postmarket, and surmised that randomization after approval will probably be less successful than it was the first time around.

Dr. Yuh stated that he is concerned about setting a precedent for suboptimal studies that could get out of hand with new devices.

Dr. Zuckerman affirmed that the guidance document on uncertainty has been carefully written to be consistent with good clinical judgment.

Dr. Vetrovec suggested that if a definitive mechanism of action could be produced, randomization may not be necessary.

Dr. Yeh adduced that many of the current treatments for these patients are on equally thin evidence bases. He stated that the data presented does not adequately convince him that this is a very efficacious device.

Dr. Ohman underscored the necessity of understanding the science and backing it up with objective evidence to show that it reduces ischemia. He cautioned that if devices become available through mechanisms that are not entirely straightforward, clinical decision making will become even harder. He added that although these patients have poor quality of life, it is essential to establish what really works.

Dr. Gersh stated that it is difficult to make decisions about efficacy on the basis of 102 randomized patients along with the other issues.

Dr. Hirshfeld asked if the Panel wants to relax criteria for breakthrough devices or if it wants to stay with a more rigorous approach for efficacy.

Dr. Starling insisted that pivotal data is needed now.

Dr. Zuckerman read a paragraph from the uncertainty guidance stating that sponsors must show, among other things, that the totality of valid scientific evidence provides a reasonable assurance of safety and effectiveness for a device.

Dr. Hirshfeld cautioned against allowing the breakthrough designation to divert attention away from safety and effectiveness.

Jacqueline Alikhaani, Consumer Representative, stated that she feels uncomfortable about the missing information and that a new trial done in the United States is essential.

Dr. Batchelor opined that it will be very difficult to do a truly effective randomized trial after approval.

Dr. Wittes remarked that if she was persuaded that the device works for quality of life and for symptoms, she would be strongly in favor of approving it.

Chairperson Lange asked for a vote by show of hands as to whether additional premarket data from a randomized sham-controlled clinical study is needed. He noted that there was one no vote and the rest were affirmative.

Debra Dunn, Patient Representative, shared her experiences as a heart failure patient. She stated that living with angina every day is very unsettling and scary. She asserted that patients want to ensure that they are safe and that whatever is put into their bodies is dependable.

Dr. Raben read Question 5b: The populations were similar between the treatment groups. The average age of subjects was 67.8 years and ranged from 35 to 87 years old. The majority of subjects (80.8%) were male and white (86.5%). The groups had comparable heart rates and blood pressure. However, the study included a limited number of female (19.2%) and minority (5.8%) patients.

The demographics of the patients enrolled in the COSIRA trial had differences compared to the U.S. refractory angina population (i.e. no black or Hispanic patients enrolled and under-representation of females). Please discuss the applicability of the study results to the U.S. refractory angina population and whether there's a need for additional clinical data of the safety and effectiveness of the Neovasc Reducer device in a more demographically representative population.

Chairperson Lange noted that the Panel believes it is necessary to have a more demographically diverse patient population.

Dr. Somberg stated that a heterogeneous population is desirable, but it has not been shown that there is more of a physiological difference in Hispanics or African Americans in this context. He specified that the important element is to include women and not to exclude microvascular disease.

Dr. Borer agreed and pointed out that there are other more essential concerns. He pointed out that if the study was adequate in other ways, the labeling could indicate that the findings are applicable to the population that was studied. He further stated that if another trial is done, every effort should be made to enhance the representation of black, Hispanic, and female patients.

Dr. Cigarroa stated that the applicability of the study results is challenging to extrapolate and there is a need for additional clinical data for effectiveness in a demographically representative population.

Dr. Batchelor cautioned against assuming there's no difference in the efficacy of medications or interventions across racial or ethnic groups because it hasn't been studied.

Chairperson Lange summarized the Panel's response:

- There is uncertainty as to whether there are mechanistically different reasons or if different genders, races, or ethnicities will respond differently and it will never be known unless it's studied.
- A study outside of the U.S. may not answer this question.

Dr. Raben read Question 5c: Acknowledging that an understanding of the Reducer's mechanism of action is not a requirement for PMA approval, please discuss the principal data supporting the intended clinical benefit in your assessment of the strengths and limitations of the data supporting device effectiveness.

If you recommend additional premarket data to support a reasonable assurance of safety and effectiveness of the Reducer, please describe the types of studies (e.g., animal or human) that would be most helpful. Please comment on and make recommendations regarding whether the recommended data could be obtained using a protocol similar to the COSIRA-II trial.

Dr. Allen stated that he is more concerned about the clinical trial design and how it was executed.

Dr. Somberg recommended having a secondary endpoint of ischemia. He stated that the mechanism is not critical.

Dr. Page expressed his hope that a pivotal study will provide better understanding of the anatomy and underlying physiology of any responses.

Dr. Gersh concluded that the pivotal study should focus on patients with obstructive coronary disease and that those patients must first be identified. He cautioned against mixing microvascular angina with microvascular dysfunction.

Dr. Mathew suggested that the mechanism of a new trial should be some subset of the population.

Dr. Starling recommended a treadmill with increase of 60 seconds in exercise time as an appropriate primary endpoint.

Chairperson Lange summarized the Panel's response:

- A robust clinical study is needed.
- Animal studies would be helpful in identifying subsets or providing mechanisms when results from the pivotal study are on the threshold.

Dr. Raben read Question 6: Given the totality of the evidence regarding the effectiveness and safety profile of the device, please comment on the benefit-risk profile of this device.

Dr. Mathew stated that it is relatively safe. He added that the benefit is modest, at best, based on the data that was presented.

Dr. Allen opined that six months seems to be a very short window to determine its safety in the intermediate term.

Dr. Cigarroa stated that it is hard for him to believe that the benefit-risk profile is favorable without further insights and additional high-quality data.

Dr. Somberg reiterated that FDA should question the use of antiplatelet agents with

this device since it sits on the venous side.

Ms. Alikhaani commented that it is not possible to do a good benefit-risk assessment without having all of the necessary information.

Dr. Yeh concluded that there's not enough certainty to say definitively that the benefit-risk profile is greater than zero.

Chairperson Lange stated that he does not think there is enough data to suggest that the device is safe. He noted that the Panel does not feel that the benefit-risk profile is favorable because of lack of confidence in the benefit.

Dr. Raben read Question 7: Please discuss and make recommendations regarding the Sponsor's proposal to perform a post-approval randomized sham-controlled trial. Please also discuss what alternative postmarket approval studies could provide the data needed to support this device.

Chairperson Lange noted that this was addressed previously by the Panel, that all but one member feels that a premarket approval study is necessary.

SUMMATIONS

Dr. Raben gave a brief rundown of key discussion topics. He noted the Agency's appreciation of the Panel's attention and review of the strengths and limitations of the data.

Dr. Stone pointed out that there are few options for patients who have exhausted coronary revascularization and antianginal medications. He highlighted the safety of the device and relative ease of the procedure, acknowledged that the dataset is not perfect, and emphasized his belief that a post-approval trial is doable and that blinding can be maintained. He then reminded the Panel of the unmet clinical need and of the device's breakthrough designation.

Dr. Henry stated that this is a challenging patient population, that they have no options, and that the treatments currently provided to them are much riskier. He further stated that the safety profiles are excellent and the risk-benefit profile is good. He also pointed out that the baseline characteristics and medications are mostly identical to those in clinical trials that have been done in the United States.

Ms. Bebeau thanked the Panel and affirmed that the company is committed to doing a postmarket REDUCER-II study.

FINAL COMMENTS

Ms. Alikhaani stated that patients need to be included in more of these kinds of discussions. She pointed out that it is necessary for physicians to have the best evidence from research to aid their patients in making informed decisions.

TEMPORARY NON-VOTING MEMBER STATUS STATEMENT

Ms. Asefa read the Appointment to Temporary Non-Voting Member Status Statement and appointed Ms. Alikhaani as a temporary non-voting consumer representative.

PANEL VOTE

Ms. Asefa read the safety and effectiveness definitions as defined in 21 C.F.R. Section 860.7. She then read the indications for use, explained the voting procedure, and read the voting questions.

Question 1: Is there a reasonable assurance that the Neovasc Reducer System is safe for patients who meet the criteria specified in the proposed indication?

The Panel voted 14 yes, 4 no, with 0 abstentions.

Question 2: Is there a reasonable assurance that the Neovasc Reducer System is effective for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 1 yes, 17 no, with 0 abstentions.

Question 3: Do the benefits of the Neovasc Reducer System outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 3 yes, 13 no, with 2 abstentions.

Chairperson Lange asked the Panel members to discuss their votes.

Dr. Vetrovec indicated that he voted yes, no, and yes. He stated that his risk-benefit vote depends on how symptomatic patients are.

Dr. Starling indicated that he voted yes, no, and no. He stated that for safety, he is comfortable with the totality of the data; for efficacy, he is not comfortable with the data from the randomized trial, the sample size, and the lack of Reducer information; and for risk-benefit, his no vote is based primarily on the lack of any convincing efficacy.

Dr. Connor indicated that he voted yes, no, and abstain. He stated that there are no big safety concerns, that efficacy is weak, and that because he is not a clinician seeing these patients, he does not feel qualified to weigh the benefit and risk.

Dr. Brindis indicated that he voted yes, no, and no. He stated that if the sponsor had opted to take on this trial when FDA offered it, things would be further along in terms of potentially helping patients with a device that could be of value.

Dr. Allen indicated that he voted yes, no, and no. He stated that there are too many issues with the trial.

Dr. Page indicated that he voted yes, no, and no. He stated that physicians need to provide patients with something that they truly believe is going to be effective, and this was not proven.

Dr. Bonde indicated that he voted yes, no, and no. He stated that there is not enough data to support effectiveness or to prove a risk-benefit ratio for these patients.

Chairperson Lange read Dr. Wittes' comments into the record: **Dr. Wittes** indicated that she voted no on all three questions. She stated that there is not enough long-term safety data and the sample size is too small to assess it even in the short term.

Dr. Yuh indicated that he voted yes, no, and abstain. He stated that the totality of the safety profile data gave him confidence in the safety of the device, that the standard for efficacy has not been met, and that although there may be a positive signal regarding risk-benefit, it was not convincing with this particular trial.

Dr. Yeh indicated that he voted yes, no, and abstain. He stated that he does not feel confident in the assessment of efficacy and that there may be a benefit, but he is unsure that it is truly there.

Dr. Batchelor indicated that he voted yes on all three questions. He stated that as a patient-centered outcome for angina only, there is a good chance that the device does work. He specified that his votes hinge on the requirement for more data.

Dr. Ohman indicated that he voted no on all three questions. He stated that there is a lack of long-term safety data, that ischemia cannot be linked with the device, and that there is no apparent risk-benefit equation that would be favorable.

Dr. Cigarroa indicated that he voted yes, no, and no. He stated that the primarily male Caucasian/European and non-U.S. approach makes extrapolation to the U.S. population very difficult, and that the small sample size has flaws and is challenging.

Dr. Hirshfeld indicated that he voted no on all three questions. He stated that the six-month safety data is too short for a permanently implanted device; that the subjective signal of efficacy is there, but weak; and the objective signal of anti-ischemia is lacking.

Dr. Mathew indicated that he voted yes, no, and yes. He stated that he would have been more amenable about efficacy if an objective secondary endpoint had been powered and met, and that the missing data is a concern.

Dr. Gersh indicated that he voted yes, no, and no. He stated that longer-term data would be beneficial and that he does not feel comfortable in assessing the risk-benefit until there is proof of efficacy.

Dr. Somberg indicated that he voted no on all three questions. He stated that the long-term data is inadequate for a permanently implanted device, that the population was not defined, and that he is not sure that the device will be effective in a drug-resistant end-stage population.

Dr. Borer indicated that he voted yes, no, and no. He stated that the long-term data are not there, that the issues surrounding antithrombotic therapy have not been worked out, and that the population was poorly defined.

ADJOURNMENT

Dr. Zuckerman thanked the panel members and commended Chairperson Lange for setting the standard as chair of the first virtual advisory panel meeting for devices.

Chairperson Lange then adjourned the meeting at 8:01 p.m.

I certify that I attended this meeting on October 27, 2020 and that these minutes accurately reflect what transpired.

James P. Swink -S Digitally signed by James P. Swink -S Date: 2021.04.16 13:52:20 -04'00'

Aden Asefa, M.P.H.
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

_____/S/_____
Richard A. Lange, M.D., MBA
Chairperson

Summary Prepared by

Karen D. Martini
Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947
November 10, 2020